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ABSTRACT

Background: Stereotactic body radiation therapy (SBRT) is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment. It has also been shown recently that many prostate cancers may be better controlled using large dose per fraction treatments such as might be delivered by SBRT. While large dose per fraction treatments are facilitated by new generation radiation delivery equipment, technology cannot independently overcome normal tissue consequences to tubular organs adjacent or within targets (e.g., the urethra and rectum for prostate cancer). As such, careful prospective clinical trials must be designed that appropriate bridge the information learned from laboratory testing, historical clinical experience, and the clinical experience with SBRT from other sites in order to test this new therapy for prostate cancer. Objective: Our goal is ultimately to carry out a prospective phase I/II trial of SBRT for treatment of localized prostate cancer such that its true efficacy and toxicity might be characterized. The objective of this application is to establish the collaborations necessary for formulating these protocols, write the protocols, assemble the clinical research infrastructure necessary for submitting the protocols, set up mechanisms for multi-center participation with our center acting as the coordinating center, recruiting, enrolling, treating and following patients, and to support the research infrastructure and clinical researchers performing these tasks Specific Aims: 1) Perform dosimetric evaluation of optimal beam geometry, beam shaping and intensity mapping in conjunction with physical maneuvers to avoid damaging dose to normal tissues. 2) Form relationships and agreements with important collaborators both at our institution and at a limited number of outside institutions that will facilitate the ultimate success of a clinical protocol. 3) Construct a protocol for testing very large dose per fraction radiation that properly selects patients, requires uniform SBRT treatment, and defines adequate follow-up toward measuring the defined endpoints. 4) Devise strategies for recruitment of the appropriate patient population for the protocol. 5) Develop a rudimentary information system capable of patient related data exchange between departments and institutions. Study Design: This development effort will employ a team approach of radiation oncologists, urologists, physicists, biologists, and research personnel to divide the tasks and carry out the specific aims. Communication will be facilitated by regular team meetings, teleconferences and training sessions organized as part of this project. Relevance: The proposed work is innovative because it can fill a large void in understanding of a treatment that shows considerable promise in treating prostate cancers. The work constitutes true translational science research conducted by researchers at the University of Texas Southwestern and our experienced colleagues at other centers. With success of the aims presented, this work will be directly translated to the clinic allowing prudent testing of this radioablative technique in a credible prospective fashion. It will serve as a springboard for further research, notably via the prospective trials, but also by

creating the infrastructure and collaborations to test other hypothesis that will be formulated as the project matures.

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Introduction

Despite several treatment options, patients with organ confined prostate cancer continue to suffer recurrence of their disease. In addition, many of the treatments available are unpalatable for groups of patients because they are too invasive, too inconvenient, or prohibitively toxic. This work involves the translation of central nervous system (CNS) radiosurgery technologies already established in radiation oncology to treat tumors outside of the brain. Such treatments are called Stereotactic Body Radiation Therapy (SBRT). It is a non-invasive therapy generally carried out in 1-5 outpatient treatments making it attractive for patients in comparison to surgical and conventional radiation alternatives. Our group has been active in translating this new treatment paradigm via prospective clinical testing in other extracranial sites including the liver, lung, and kidney. This is a biologically distinct therapy from conventional fractionated radiation therapy, and there are strong biological incentives to use the therapy in prostate cancer. Still, there are unique anatomical and functional relationships of the surrounding normal tissues in the pelvis that will make use of this therapy in prostate cancer potentially problematic. We have chosen a strategy to couple our previous clinical experience and preclinical animal testing done at our center to develop a trial allowing the best opportunity to succeed in controlling localized prostate cancer. If this therapy is ultimately efficacious and safe, it will constitute and much more convenient non-invasive outpatient therapy as compared with current treatments. This work involves developing a phase I and II trial of SBRT in localized prostate carcinoma. The therapy will initially involve a phase I study using three fractions of very large dose treatments. Subsequently a Phase II study will validate toxicity and look for efficacy in a larger patient population. The trial has been written and IRB approved. A companion translational research study has also been written. This is a multi-institutional trial. We think there is considerable promise with this approach, and the protocol and translational studies we developed should serve as a legitimate test of this new therapy.

Body

The statement of work submitted for this project went as follows:

Task 1. Form relationships and agreements with important collaborators including basic scientists, urologists, radiation oncologists, research nurses, data managers, statistical collaborators, and other support personnel both at our institution and at a limited number of outside institutions that will facilitate the ultimate success of a clinical protocol for organ confined prostate cancer. If necessary, collaborations will be formed with pharmaceutical companies or medical device companies as well (months 1-6).

Task 2. Construct a protocol for testing large dose per fraction radiation delivered stereotactically that properly selects patients, requires uniform treatment, and defines adequate follow-up toward measuring the defined endpoints (months 1-10).

a. Write body in a straightforward and scientifically valid fashion
b. Obtain consultation with medical statisticians to ensure study designs are valid
c. Interact with collaborating institutions to avoid multiple submissions
d. Send protocol and consent through review processes including IRB

Task 3. Devise strategies for recruitment of the appropriate patient population for the protocol (months 6-12).

Task 4. Develop an rudimentary information system capable of patient related data exchange between departments and institutions (in a HIPPA compliant fashion) including information related to patient demographics and characteristics, treatment dosimetry (including a means for quality assurance evaluation), and capture of follow-up data (months 9-12).

Task 1:

The key relationships were formed as described. We concluded that the clinical trial must be multi-centered and take place in centers with appropriate demographics. We are targeting patients from rural or remote areas such and farmers and ranchers. Our center in Dallas can capture such patients within Texas. At UTSW, we have strong support from the PI, Dr. Timmerman, in radiation oncology, Dr. Yair Lotan, a urologist with a busy prostate cancer practice and interest in SBRT (as evident by two publications in urological journals), and Dr. Michael Story, a radiobiologist with expertise in proteomics and tissue archiving. We also recruited the statistical help for the study by enlisting Dr. Suzanne Swann, head statistician for the RTOG, as the clinical and translational protocol statistician. We formed clinical collaboration with Drs. Brian Kavanagh (radiation oncology) and E. David Crawford (urology) from the University of Colorado. Finally, we formed clinical collaboration with Drs. L. Chinsoo Cho (radiation oncology) and Kenneth Koeneman (urology). We had conference calls and met face to face to agree on the trial design, selection, treatment conduct and follow-up. We had tried to collaborate with the Princess Margaret Hospital as outlined in our grant application. However, this did not work out due to competing interests with other trials. We agreed as to how patients would be recruited as well as target accrual numbers for each participating institution.

The translational science aspect of the study goals were built into a companion trial. This companion trial was written to be carried out on patients treated at UTSW. This trial is voluntary and only offered to patients already eligible and enrolled to the clinical trial. As there is solid evidence that the presence of hypoxia correlates with biochemical failure, we chose to carefully study hypoxia in our patients. In addition, basic and translational scientists at UTSW are recognized leaders in measuring and assessing the effects of hypoxia in prostate cancer. We formed collaboration with Dr. Ralph Mason in radiology as well as Dr. Robert Sims. Dr. Mason is a recognized expert in hypoxia assessment using MRI and other methods. Dr. Sims is an MRI radiologist. For the companion protocol we propose to first measure the oxygenation status of patients and then assess dynamic changes that may correlate with outcome. Our hypothesis is that degree of initial hypoxia or failure to re-oxygenate may correlate with poorer outcome in the clinical study. One of the measures of hypoxia that we chose to use is pimonidazole staining. As this is an investigational drug, we sought and secured collaboration with Drs. James Raleigh and Mahesh Varia from the University of North Carolina to operate this study under their IND.

Task 2:
The clinical protocol was written and circulated to all participating institutions. It is attached in the appendix of this report. It is IRB approved. The approval letter is attached in the appendix. The UTSW clinical research office will manage the trial. A data safety monitoring plan has been devised. The companion protocol was written to be carried out at UTSW. It's implementation will depend on funding. A grant application was submitted to the US Department of Defense for a Clinical Trial Award. We are awaiting the review and Summary Statement for that grant. The grant would fund both the clinical trial and companion protocol.

Task 3:
Our first recruitment strategy was to open the trial at centers both experienced in clinical trials and typically seeing farmers and ranchers. The population seen at UTSW, University of Colorado, and University of Minnesota fit this description. Second, we will submit the trial to the NIH to be approved by CTEP and posted on their website. Third, we are enlisting the help of Dr. Kevin McGee at UTSW who previously owned a company that provided specialized care for fetal-maternal medicine in remote areas. Dr. McGee is providing a roadmap for how to make contacts and secure referrals that proved successful in building his company. We have developed a slide set presentation to be presented at rural hospital tumor boards by the investigators and are setting up dates. We are also exploring direct mailings and newspaper advertisements, but this will require approval by the IRB.

Task 4:
We have developed standard forms for eligibility assessment, treatment QA, and follow-up. These forms will be used initially and sent by mail. We have not finalized but are exploring a web based entry. Our institution's IRB has not had experience with this outside of the cooperative groups and has not given approval. We have planned interim QA assessments to insure the treatments are uniform. To that end, we have circulated practice plans to cross critique among the participating centers. We have agreed on the type of rectal balloon to be used at all centers. We have agreed on the methods of contouring and written them into the protocol.

Key Research Accomplishments

As this grant funded a clinical trial development award, the main goal was to create a legitimate protocol. In addition, the grant expected that a subsequent grant application be submitted to fund the actual clinical trial. Both of these major goals were accomplished. The clinical trial was developed among several institutions, a companion translational science protocol was developed, and a grant submission to the DOD was made last month. The protocols are in the appendix. Our group at UTSW published two papers relating to SBRT dosing for genitor-urinary cancer. Our group at UTSW hosted an international symposium in Dallas on SBRT translational research which attracted150 participants. That symposium facilitated forming our relationships for hypoxia research.

Reportable Outcomes

This grant related to the development of a clinical trial. The reportable outcomes are the protocols and the grant submission. We attach the protocols in the appendix. The grant submission to the Department of Defense Clinical Trials in Prostate Cancer program is very long and is not included but we will forward if requested.

Conclusions

Stereotactic body radiation therapy has been tested in several disease sites with promising results. Unfortunately, it is being used beyond prospectively designed trials or in indications outside of what was tested in previous prospectively designed trials. Indeed, sites are using SBRT in prostate cancer despite a lack of validated effects both to control the cancer or assess toxicity. This work aimed to design a valid clinical trial as well as set up a plan to understand basic mechanisms of large dose per fraction radiation treatment. We accomplished the tasks of identifying a population not-so-well served by current treatments, organized a trial at several centers, came to consensus on selection and endpoints, set up a hypothesis driven translational endpoint, and wrote a grant to secure future funding to make it all possible. In this way, SBRT will be legitimately tested to see if there is value in this therapy for treating prostate cancer.

References

None

Appendices

Attached is the following:

1. Clinical Trial for using SBRT in treating localized prostate cancer.
2. Translational companion trial for assessing the effect of hypoxia in the study population.
3. IRB approval letter
4. Grant submission impact statement for Clinical Trial Award in Prostate Cancer (submitted 6/06)

Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

Organizing Institution:
University of Texas Southwestern Medical Center
Principal Investigator (P.I.): Robert Timmerman, M.D.
Department of Radiation Oncology

Co-Investigators: Yair Lotan, M.D.
Department of Urology

Michael Story, Ph.D.
Department of Radiation Oncology

Suzanne Swann, Ph.D.
Biostatistics

Affiliated Institutions:
University of Minnesota
Principal Investigator (P.I.): L. Chinsoo Cho, M.D.
Department of Radiation Oncology

Co-Investigators: Kenneth Koeneman, M.D.
Department of Urology

University of Colorado
Principal Investigator (P.I.): Bryan Kavanagh, M.D.
Department of Radiation Oncology

Co-Investigators: E. David Crawford, M.D.
Department of Urology

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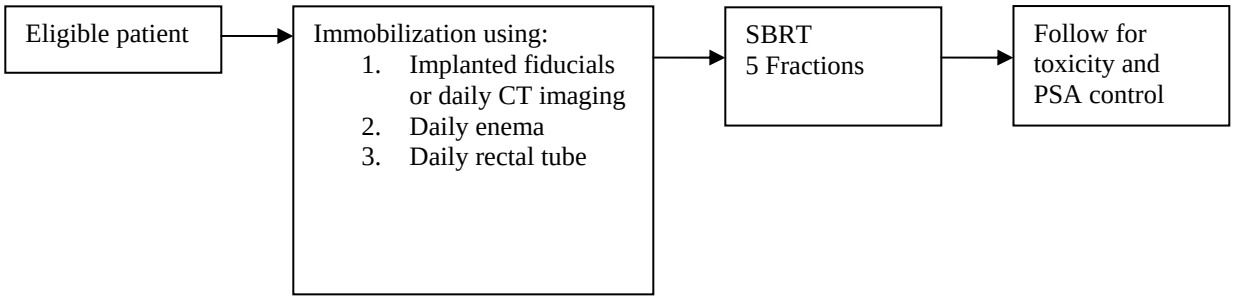
Synopsis

Schema



Number of patients = between 5-54 for phase I (depending on tolerance)
= 50 for phase II

Phase I

Patients in each dose cohort will all be treated as a single group for dose escalation. The starting dose for the dose escalation portion will be 9 Gy per fraction for 5 fractions (total dose = 45 Gy). Subsequent cohorts of patients will receive an additional 1 Gy per treatment (total 5 Gy per escalation) as follows:

No. Fractions	Dose per fraction (Gy)	Total Dose (Gy)	No. Patients
5	9	45	5-9
5	10	50	5-9
5	11	55	5-9
5	12	60	5-9
5	13	65	5-9
5	14	70	5-9

Minimum waiting periods will be assigned between each dose cohort to observe toxicity. The phase I portion of the study will be completed when dose limiting toxicity is reached or when a sufficiently high dose level (at least 12 Gy per fraction), at the investigators' discretion, is attained to consider the therapy likely to be efficacious.

Phase II

Additional patients will be treated at either the maximum tolerated dose (MTD) or at the efficacious dose level as determined by the investigators from the Phase I portion of the study. The phase II study will evaluate efficacy endpoints with larger patient numbers and continue to build the toxicity profile of this regimen following the phase I study.

Eligibility

Signed study specific informed consent form.
Gleason score ≤ 7
PSA ≤ 20 ng/ml prior to hormone therapy (if given) for Gleason 2-6
PSA ≤ 15 ng/ml prior to hormone therapy (if given) for Gleason 7
T1a, T1b, T1c, T2a, T2b
Up to 6 months of previous hormonal therapy is allowed (but not required)
Adenocarcinoma of the prostate

Age ≥ 18
Zubrod Performance Status 0-2

Ineligibility

Positive lymph nodes or metastatic disease from prostate cancer
T2c, T3, or T4 tumors
Previous pelvic radiotherapy
Previous surgery or chemotherapy for prostate cancer
Hormonal therapy given for more than 6 months prior to therapy
Previous transuretheral resection of the prostate (TURP) or cryotherapy to the prostate
Plans for concurrent or post treatment adjuvant hormonal therapy or chemotherapy
Concomitant antineoplastic therapy (including surgery, cryotherapy, conventionally fractionated radiotherapy, and chemotherapy) while on this protocol.
History of Crohn's Disease or Ulcerative Colitis.
No significant obstructive symptoms; AUA score must be ≤ 15 (alpha blockers allowed)
No major psychiatric illness
Men of reproductive potential may not participate unless they agree to use an effective contraceptive method.
Ultrasound estimate of prostate volume > 60 grams

Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT)
for Low and Intermediate Risk Prostate Cancer

ELIGIBILITY CHECKLIST

Case # _____ (page 1 of 2)

_____(Y) 1. Prostate adenocarcinoma histologically confirmed by biopsy?

2. What is the TNM-Stage?
_____(T1a, T1b, T1c, T2a, OR T2b)
_____(N0)
_____(M0)

_____(≤PSA)3. What is/was the serum Prostate-Serum Antigen (PSA) prior to any hormonal therapy (if given)? (PSA ≤ 20 ng/ml for Gleason 2-6 and ≤ 15 ng/ml for Gleason 7)

_____(≤ 7) 4. What is the Gleason score from the prostate biopsy?

_____(N) 5. Does the patient have history of significant inflammatory colitis (e.g., Crohn's Disease or Ulcerative colitis)?

_____(≥ 18) 6. How old is the patient (in years)?

_____(0-2) 7. What is the patient's Zubrod performance status?

_____(Y) 8. Has the patient agreed to use an effective method of contraception if able to have children?

_____(Y) 9. Have the required pretreatment evaluations and staging studies been obtained?

_____(Y/N) 10. Has the patient had prior hormonal therapy?
_____(N) If yes, was more than 6 months of therapy given prior to study entry?

_____(N) 11. Any prior chemotherapy or surgery for prostate cancer?

_____(N) 12. Any prior radiotherapy to the pelvis?

_____(N) 13. Are other concomitant cancer therapies planned including surgery, cryotherapy, chemotherapy, or conventionally fractionated radiotherapy?

_____(N) 14. Has the patient undergone previous transurethral resection of the prostate (TURP) or cryotherapy to the prostate?

_____(Y/N) 15. Has the patient had a previous or concurrent cancer (excluding basal/squamous cancers of skin or in situ cancer)?
_____(Y) If yes, has the patient been disease free for > 3 years?

_____(Y) 16. Is the patient's AUA score ≤ 15?

_____(N) 17. Is the patient's ultrasound estimate of the prostate volume > 60 grams?

_____ (Y) 17. Has the patient signed the protocol consent?

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Localized Prostate Cancer

There were 232,000 new cases of prostate cancer diagnosed in the United States in 2005 and 30,000 deaths [1]. Among males, prostate carcinoma was the 2nd leading cause of cancer mortality behind lung cancer and ahead of colo-rectal cancer. The incidence of early stage prostate cancer rose dramatically in the US with the onset of widespread use of prostate-specific antigen (PSA) blood test screening. Levels have continued to increase but more slowly in men younger than 65, but have leveled off in men older than 65 since 1995. Death rates have remained level or decreasing since the mid 1990s, presumably from earlier detection with PSA screening. The main risk factors are age, ethnicity, and family history. Up to 70% of all prostate cancers are diagnosed in men greater than 65 years old which impacts therapy options as a result of competing co-morbidities. Men of African decent have the highest incidence of prostate cancer while men in North American have higher incidence than men in Asia and South America. Familial disposition may account for 5-10 percent of prostate cancers. Early detection of the disease appears to account for improvements seen in the US cause-specific mortality rate. The American Cancer Society recommends annual screening PSA testing and digital rectal examination (DRE) in all men starting at age 50 (starting at age 45 in high risk men) in order to allow diagnosis of cancer while still organ confined. With this approach, overall 5-year survival has improved from 67% in 1974 to nearly 100% in 2000; however, cancer specific survival continues to decline after five years due to the long natural history and lack of cancer control in many men.

Radiotherapy options for organ confined prostate cancer have included protracted radiation in the form of external beam delivered over 7-10 weeks of daily therapy (including 2-D, 3-D conformal, and intensity modulated radiation therapy or IMRT) [2-4] and also permanent brachytherapy seed implantation using iodine or palladium [5-7]. Treatments have also been delivered using shorter overall treatment times. These include hypofractionated external beam treatments and high dose rate (HDR) brachytherapy implants [8-11]. In addition to being more convenient for patients with fewer trips to the treatment facilities, these treatment options completed over a shorter period have unique long term effects in both tumor and normal tissues. Depending on the relative differences between tumor response and normal tissue injury, the timing in which radiotherapy is delivered may have significant impact on the therapeutic ratio (benefit/toxicity). A commonly used mathematical model used to describe these effects has been the “linear-quadratic” model proposed by Douglas and Fowler [12]. In this model, the log survival vs. dose relationship is modeled by an arithmetic power series truncated to the linear and quadratic terms. The linear coefficient in this progression is commonly called “alpha” while the quadratic coefficient is called “beta.” It has also been proposed that the linear term described by alpha corresponds to the more infrequent effect of double strand breaks within tissue DNA caused by radiation which disable the clonagenicity of the cell with little chance of repair. In turn, the beta term reflects the consequence of more than one single strand break in close enough proximity on the DNA to disable the cell. These single strand breaks occur much more frequently than double strand breaks, but they may be more readily repaired unless they happen so frequently that repair mechanisms become overwhelmed such as might occur with large dose per fraction radiation. Hence, at low dose per fraction, alpha events dominate the cellular response while at large dose per fraction, beta events become more important. These events occur, at different rates and proportions, in both tumor and normal tissues exposed to radiation.

It has been commonplace to describe tissue response properties of various tissues toward radiation by their alpha to beta ratio. The alpha and beta values may be measured *in vitro* by exposing cell cultures to varying doses and schedules of radiation. Normal tissues, more capable of repairing radiation injury, typically have a lower alpha/beta ratio in the order of 2-3. Common cancers of the lung, cervix and head and neck are quoted to have alpha/beta ratios in the 10 range. For such tumors, exploitation of the differences between normal tissue and tumor response has led radiation oncologists to use more protracted courses of radiation using small daily doses to high total cumulative doses (so-called conventional fractionation, e.g., 2 Gy per fraction to a total dose of 70-76 Gy). Prostate cancer cell lines have been difficult to grow in tissue culture and therefore there has been less direct evidence of the alpha/beta ratio. It was generally assumed to be similar to epithelial malignancies of the gastrointestinal and bronchopulmonary tract leading to the conventional dose fractionation schedules used in clinical practice or the low dose rate implants used in permanent prostate seed brachytherapy. More recent evidence, however, has implied that the alpha/beta ratio for prostate cancer may be much lower than expected. In fact, using outcome data of patients treated with different dose fractionation schemes (in vivo), it has been suggested that the alpha/beta ratio for prostate cancer may be as low as 1.5-3 which is perhaps even lower than the surrounding normal tissues. If this were true, there would be no advantage to protracted radiotherapy schedules. This realization has led to several investigations of much shortened radiotherapy schedules. Of course, the shortest radiotherapy schedules of all have been SBRT treatment schedules which is the impetus for this protocol.

Several investigators at a variety of institutions have investigated using modestly larger dose per fraction treatment schemes as compared to conventional fractionated radiotherapy [references]. For example, in a mature prospective experience reported by Livsey and colleagues from England, 50 Gy total in 3.13 Gy fractions produced PSA control rates comparable to published reports using 70 Gy with 2 Gy fractions [13-14]. In addition, they found the treatment carried out with 3-D conformal techniques was well tolerated. That same group is carrying on the research using 3 Gy per fraction, 60 Gy total dose, and intensity modulated radiation therapy (IMRT) techniques in an effort to improve PSA control rates [11]. In the US, Kupelian and colleagues used 2.5 Gy per fraction and published mature results to 70 Gy total dose in 5.5 weeks [10]. Their patients also had good PSA control rates and acceptable rates of toxicity, especially if the volume rectum getting 70 Gy is limited to 10 cc. Similar investigations are now being planned or carried out for larger groups of patients in cooperative group trials. Altogether, these trials show that the treatment can be delivered much more quickly and conveniently using hypofractionation without compromising PSA control or toxicity so long as careful technique is respected.

1.2 Stereotactic Body Radiation Therapy (SBRT)

'Stereotactic radiosurgery' generally refers to a procedure design to treat deep-seated brain tumors or abnormalities, and is commonly performed on a specialized machine, such as the Gamma Knife. This procedure involves immobilizing the patient (cranial halo), affixing a stable 3-D coordinate system (feducial box and head frame), performing high resolution imaging (CT or MRI), registering the images to the coordinate system using a computer, virtually simulating delivery of very focal and conformal dose profiles of radiation with steep dose gradients toward normal tissue, and finally carrying out the treatment with sub-millimeter accuracy. Typically very high doses of radiation (15-40 Gy) are given in a single treatment with this technique. Any adjacent normal tissues that receive this dose may be significantly damaged, thus the requirement for very conformal treatments with rapid dose fall-off. An alternate strategy has been to divide total radiation dose into two or three

fractions, still with fairly large dose per fraction (6-10 Gy), attempting to decrease adjacent normal tissue toxicity. These fractionated techniques are referred to as 'stereotactic radiotherapy,' and are carried out with hope that surrounding normal tissue will tolerate the treatment as a result of relatively more successful sublethal damage repair as compared to tumor.

Translation of the stereotactic radiosurgery and radiotherapy concepts to extracranial sites has not been straightforward [15-17]. With brain treatments, the skull serves as an excellent surface to rigidly couple the immobilization frame using stainless steel pins under local anesthesia. Once the skull is immobilized, targets within the skull are likewise immobilized in that there is very little movement of intracranial structures outside of fluid waves around the ventricles. Such is not the case for extracranial sites. Inherent motion, such as the heart beating, lungs expanding and emptying, and bowels churning results in movement of potential targets. In addition, the external surface anatomy does not have structures amenable to rigid fixation to a frame. In 1994, Lax, et al, from the Karolinska Hospital in Sweden reported on the development and testing of an extracranial frame that incorporated a feducial stereotactic coordinate system along its side panels [18]. The system used vacuum pillows to make contact with three sides of the patient (maximizing surface area of contact) and correlation of external anatomical reference points on the sternum and calf for immobilization. To decrease respiratory excursion, an abdominal press was employed forcing the patient to perform relatively more chest wall rather than diaphragmatic breathing. A formal verification of reproducibility study was carried out, and target motion was reduced to within 0.5 cm in the axial plane and 1.0 cm in the caudal/cephalad plane. With this degree of accuracy (compared to 0.05 cm target position accuracy for the Gamma Knife), stereotactic radiosurgery could not be performed; however, they did set up a program treating patients with extracranial stereotactic radiotherapy.

Stereotactic body radiation therapy (SBRT) is a new therapeutic paradigm for treating localized tumors outside of the central nervous system and involves delivering very high doses of focused radiation using unique beam arrangements and special immobilization equipment [19]. As already demonstrated in lung and liver cancers, these treatments offer hope for improved local control of cancers that may translate into gains in survival especially for smaller early stage lesions. SBRT employs daily treatment doses dramatically higher than typical for conventionally fractionated radiation therapy (CFRT). In turn, it is incorrect to assume that SBRT radiobiology is similar to historical CFRT. Indeed, a unique biology of radiation response for very large dose per fraction treatments is being appreciated both in terms of tumor control as well as normal tissue consequences translating into unique clinical outcomes. For example, local control with CFRT in early stage lung cancer is consistently reported below 50% while several series using SBRT show local control around 90% [20-21].

SBRT has been defined by the American College of Radiology (ACR) and American Society of Therapeutic Radiology and Oncology (ASTRO) to involve the use of very large dose per fraction [22]. Indeed, dose per fraction of 8 Gy minimum would obviously make SBRT very different from even the more abbreviated hypofractionation schemes described above. Typically, only 1-5 fractions are used for SBRT depending on the tolerance of adjacent or intervening normal tissues. Linear structures (like the spinal cord) and tubular structures (like the bowels) are commonly called "serially functioning tissues" akin to series electrical circuits because their function is disrupted if there is a defect anywhere along their pathways [23-24]. It has been shown that serial functioning tissues are less tolerant to SBRT than so-called "parallel functioning tissues" like the peripheral lung and liver. In response, typically more fractions are employed (e.g., five fractions rather than one) when serially functioning

tissue cannot be avoided. In the case of treating prostate cancer, the rectum is an adjacent serially functioning tissue while the urethra is an intervening serially functioning tissue traversing the very center of the prostate target.

1.3 Current Protocol

Prostate cancer has several good treatment options for organ confined disease such as surgery and conventional radiation. In addition, some men with indolent disease are appropriately treated with watchful waiting. However, all of the established treatments continue to fail in a portion of patients via tumor recurrence. Furthermore, current treatments are often unpalatable for many patients because they are either too invasive or too inconvenient. It has also been shown recently that many prostate cancers may be better controlled using large dose per fraction treatments such as might be delivered by stereotactic body radiation therapy (SBRT). While large dose per fraction treatments are facilitated by new generation radiation delivery equipment, technology cannot independently overcome normal tissue consequences to tubular organs adjacent or within targets (e.g., the urethra and rectum for prostate cancer). As such, careful prospective clinical trials must be designed that appropriately bridge the information learned from laboratory testing, historical clinical experience, and the clinical experience with SBRT from other sites in order to test this new therapy for prostate cancer. This is an important problem, since localized prostate continues to recur despite current treatments and more effective, less toxic and more convenient treatments are necessary.

As the SBRT therapy is strictly local, we will select for patients with prostate cancer locally confined to the prostate gland. As such, we will select eligibility criteria sanctioned in the past by the Radiation Therapy Oncology Group to predict a reasonably low risks of both extraprostatic capsular extension and seminal vesicle invasion. We will apply the Roach formula to limit eligibility to patients with under a 20% risk of pelvic lymph node involvement. Some patient eligible for this trial may have a somewhat higher risk of extraprostatic spread (e.g, T2b, Gleason 7 or PSA>10) and it will be allowed to use pre-treatment hormonal therapy in such patients at the investigator's discretion. Hormonal therapy may also be used to shrink prostates that are massively enlarged. As the primary toxicity will likely be mucosal damage, we will avoid enrolling patients with pre-existing mucosal dysfunction (including those with previous radiation, TURP, very large prostate glands, and inflammatory bowel disease). In this way, patients will be uniformly selected in a fashion that would identify patients likely to receive benefit from the therapy.

As the most efficacious SBRT dose for treatment of the prostate has not been prospectively identified, we will start with a careful phase I dose escalation toxicity study. Patients enrolled at each dose level will undergo routine evaluations to identify potential toxicities. Adequate waiting periods will be respected to insure dose escalation does not proceed prior to observing toxicity. When the MTD is determined or the dose reaches a significantly high level expected to be both tumoricidal and able to control PSA by the investigators, subsequently enrolled patients will be accrued into the phase II portion. In the phase II portion, further patients will be accrued to confirm toxicity data on a larger scale, and attempt to characterize whether there is enough beneficial effect in this population to warrant further clinical testing.

We will use a treatment regimen carried out in 5 total fractions. This would be a more tolerant regimen than our 3 fraction regimens published in liver and lung cancer [25-26] and may lessen the toxicity to serial functioning tissues in close approximation to the prostate

(rectum and urethra). Given there will be only 5 treatments, daily enemas, rectal tubes, and even urethral catheters are all feasible undertakings that may help optimize the therapy.

It is predicted that the dose limiting toxicity from this treatment will likely relate to urethral dysfunction (e.g., ulceration, bleeding, pain, narrowing and frank stricture) and rectal damage (ulceration, bleeding, chronic inflammation, and pain). Since the radiotherapy target for radiotherapy of the prostate is the entire gland, the urethra will by definition be situated toward the center of the target thereby receiving the target margin dose at a minimum. In fact, the urethra may receive even a higher dose than the minimum target dose owing to the fact that SBRT dosimetry commonly includes a 10-30 percent higher central dose within the target. While wedges and other methods of modulation (including IMRT) may be used to steer this higher dose away from the visualized urethra, these techniques will have limited ability to protect the urethra. The prostatic urethra will likely be significantly damaged which may limit dose escalation. If it has the ability to heal by second intention as it has been shown to do after other severe insults such as transurethral resection without forming a diffuse untreatable stricture, the treatment may still be feasible. Certainly if mucosal clonagens can migrate from the bulbous urethra and bladder to "rescue" the prostatic urethra after SBRT, care will be taken to spare dose to those structures [24]. In regard to the rectum, the treatments will be carried out with a rectal tube to separate much of the circumference of the rectal wall from the prostate target. This rectal tube must be positioned appropriately above the anus and extend superiorly to above the prostate to be effective. In addition, the rectum should be evacuated of feces to avoid confounding the geometry prior to each treatment. If the dose to the rectum is tightly confined to the anterior wall next to the target, it is hoped that the ulcer likely to be produced will heal by recruitment of clonagens and blood supply from the lateral and posterior walls. Indeed, a precedent for assuming such a process exists with the reported treatment of small rectal cancers using an endorectal orthovoltage tube by Papillon and colleagues [27]. In that experience, doses as high as 150 Gy were given in as few as 4 fractions which undoubtedly resulted in ulceration at the point of treatment but still no reported long term untoward toxicity owing to the extremely localized high dose dosimetry.

1.4 Who Would Benefit from this Treatment?

As noted above, there are several quite good but not perfect treatments for organ confined prostate cancer that have significant follow-up and published experience as well as an option for watchful waiting. Still, there are populations that might find the invasiveness of surgery and brachytherapy implants less ideal and the inconvenience of IMRT and 3-D conformal therapy impractical. General anesthesia is inappropriate for some patients due to significant co-morbid conditions. We believe a very abbreviated, non-invasive, outpatient treatment would be considered a favorable option in particular to the underserved populations of men living in more remote areas including farmers, ranchers, and those in rural communities. Furthermore, if the concept of prostate cancer having a very low alpha to beta ratio discussed previously is confirmed, this treatment using SBRT may in fact be a better option for some men with prostate cancer.

1.5 Starting Dose for the Phase I Study

There has been experience published or presented to indicate the appropriate starting dose for the phase I study. Direct evidence of tolerance by a similar treatment strategy has been presented by Madsen and colleagues from Virginia Mason University where 33.5 Gy in 5 fractions of 6.7 Gy were delivered using SBRT in men with early stage prostate cancer [28]. That dose was tolerated without grade III or higher toxicity, but had rather poor PSA control

[personal communication, Berit Madsen, M.D., 5/05). Although not using SBRT techniques, Collins and colleagues used a 6 fraction regimen to 36 Gy at 6 Gy per fraction with more conventional external beam delivery techniques which again was well tolerated [29-30]. A similar but more invasive treatment approach to SBRT is the high dose rate (HDR) implant experience which gives large dose per fraction treatments on a daily basis through implanted brachytherapy catheters. Indeed the heterogeneous target dosimetry is similar in many ways to SBRT. While HDR has mostly been used as a boost treatment after conventional external beam treatment, there is institutional data from Martinez and colleagues using HDR as monotherapy. That group at the William Beaumont Hospital used a 4 fraction regimen of 9.5 Gy to a total dose of 38 Gy and published an acceptable toxicity profile in treated patients [31-32]. Grills, et al. reported an update of these results of HDR monotherapy for the management of 65 patients with T1a-T2b, and total Gleason Score 7 or less. The preliminary biochemical PSA control rate was 98% at 3 years and it was similar to their experience with standard ^{103}Pd low dose rate brachytherapy [40]. In a similar experience using HDR, Yashioka and colleagues from Japan used higher total doses up to 48-50 Gy in 6 Gy fractions as monotherapy for localized prostate cancer without untoward toxicity [33-34]. Considering all of these experiences as basis for dose selection, we will use a starting dose of 9 Gy per fraction and deliver a total of 5 fractions to a total dose of 45 Gy. Subsequent dose levels will require a modest dose per fraction escalation of 1 Gy (e.g., 9 Gy to 10 Gy to 11 Gy per fraction, etc). We hope to reach as high of biologically potent dose as possible without exceeding tolerance (i.e., a 2 Gy equivalent dose of at least 100 Gy) that would be delivered in around 2 weeks rather than 10-12 weeks as would be required with conventional fractionation.

2.0 OBJECTIVES

2.1 In phase I, to the primary objective is to escalate the dose of stereotactic radiotherapy to a tumorcidal dose without exceeding the maximum tolerated dose in patients with organ confined prostate cancer.

2.2 In phase I, a secondary objective is to determine the dose-limiting toxicity (if the maximum tolerated dose is reached).

2.3 In phase II, the primary objective is to determine the late severe grade 3-5 GU and GI toxicity from 270-540 days (i.e., 9-18 months) from the start of the protocol treatment. It is graded based on CTCAE v3.0.

2.4 In phase II, secondary objectives will be to determine the 2 year biochemical (PSA) control (freedom from PSA failure), disease free and overall survival, local control, freedom from distant metastases, and the incidence of high grade adverse events of any type from the therapy in the treated patients in order to determine if the therapy is promising enough for further clinical investigation.

3.0 PATIENT SELECTION

3.1 All patients must be willing and capable to provide informed consent to participate in the protocol.

3.2 Eligible patients must have appropriate staging studies identifying them as AJCC stage T1 (a, b, or c) or T2 (a and b only) adenocarcinoma of the prostate gland. The patient should not

have direct evidence of regional or distant metastases after appropriate staging studies. Histologic confirmation of cancer will be required by biopsy.

3.3 The patient's Zubrod performance status must be 0-2

3.4 The Gleason score should be less than or equal to 7

3.5 The serum PSA should be less than or equal to 20 ng/ml prior to starting hormonal therapy (if given) for patients with Gleason score 2-6. For patients with Gleason score 7, PSA should be less than or equal to 15 ng/ml prior to starting hormonal therapy (if given). As such, the risk of pelvic lymph node involvement according to the Roach formula would be under 20%.

3.6 Eligible patients should not have had previous pelvic radiotherapy or have had chemotherapy or surgery for prostate cancer. Hormonal therapy given for up to 6 months prior to SBRT is allowed as a neoadjuvant therapy or to downsize the prostate gland.

3.7 There must be no plans for the patient to receive other concomitant or post treatment adjuvant antineoplastic therapy while on this protocol including surgery, cryotherapy, conventionally fractionated radiotherapy, hormonal therapy, or chemotherapy given as part of the treatment of prostate cancer.

3.8 Patients should not have undergone previous transurethral resection of the prostate (TURP) or cryotherapy to the prostate.

3.9 Patients must be past their 18th birthday at time of registration.

3.10 Patients with history of inflammatory colitis (including Crohn's Disease and Ulcerative colitis) are not eligible.

3.11 Patients may have used prior hormonal therapy, but it should be limited to no more than 6 months or therapy prior to enrollment.

3.12 Patients should not have significant urinary obstructive symptoms; AUA score must be ≤ 15 (alpha blockers allowed).

3.13 The ultrasound based volume estimation of the patient's prostate gland should not be greater than 60 grams.

3.14 Patients should not have a history of significant psychiatric illness.

3.15 Men of reproductive potential may not participate unless they agreed that they or their partner use an effective contraceptive method such as condom/diaphragm and spermacidal foam, intrauterine device (IUD), or prescription birth control pills.

3.16 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (e.g., carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible).

3.17 Severe, active co-morbidity, defined as follows:

3.17.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months

3.17.2 Transmural myocardial infarction within the last 6 months

3.17.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration

3.17.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration.

3.17.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.17.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 History and physical examination to include digital rectal examination of the prostate, determination of AUA score, and completion of EPIC prostate quality of life questionnaire.

4.1.2 Zubrod performance status (Appendix II)

4.1.3 Lymph node evaluation performed within 90 days prior to registration by either CT or MRI (lymph node dissection is acceptable but not required).

4.1.4 Prostate Specific Antigen (PSA) prior to treatment (prior to hormonal therapy, if given)

4.1.5 See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.

4.2 Highly Recommended Evaluations/Management

Cystoscopy, if advised by the urologist, may be performed to check for urethral damage including strictures, bladder pathology, or a large median prostate lobe.

5.0 REGISTRATION PROCEDURES

5.1.1 *Preregistration Requirements for diagnostic pathology review*

There are no requirements for central review of pathology used for initial diagnosis.

5.1.2 *Pre-Registration Requirements for SBRT Treatment Approach*

In order to utilize SBRT in this protocol, the institution must have met technology requirements and have provided a description of techniques, methods, training, and experience showing competency to the study PIs.

5.2 *Registration*

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met.

5.2.2 Dial-in Registration

Patients can be registered only after eligibility criteria are met. To register a patient, an investigator will call the clinical research office in the Department of Radiation Oncology at The University of Texas Southwestern Medical Center at 214-648-7034. Prior to

registration, participating investigators and institutions should review the eligibility checklist and confirm eligibility.

5.3 *Accreditation*

5.3.1 Institutional Processes

Prior to treating patients on protocol, the institution's specific methods for immobilization (e.g., frame vs. frameless), targeting, dose construction, daily verification of accuracy, ongoing assessment of accuracy and Quality Assurance policies must be described to and approved by the study PI and other approved institutional PIs. The primary purpose of accreditation will be to insure that dose is delivered to the targets and avoiding normal tissues according to protocol criteria. This accreditation may be assessed by written documentation, conference calls, or direct observation via site visits. Additional data may be required of institutions to verify that techniques are performing as intended.

6.0 RADIATION THERAPY

6.1 Dose Specifications

6.1.1 *Stereotactic Targeting and Treatment*

The term "stereotactic" for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space guided by one or several fiducials of known 3-D coordinates. This differs from conventional radiation therapy in which therapy is directed toward skin marks or bony landmarks and assumed to correlate to the actual tumor target based on a historical simulation. It should be understood that Stereotactic Body Radiation Therapy (SBRT) has become a treatment that is well beyond just stereotactic targeting. Indeed SBRT is mostly about ablative range dose per fraction, accounting properly for errors including motion, careful construction of dosimetry that compacts high dose into the tumor and not normal tissues, and extra careful treatment conduct. This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radio-opaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g. acquiring tomographic views of the tumor simultaneously with the treatment). Metallic "seeds" or markers placed within the tumor will be allowed so long as they are not prone to migration movement.

6.1.2 *Dose Fractionation*

Patients will receive 5 fractions of radiation. A minimum of 36 hours and a maximum of 8 days should separate each treatment. No more than 3 fractions will be delivered per week (7 consecutive days). Total dose will depend on the phase of the study (see schema).

6.1.3 *Premedications*

Unless contraindicated, it is recommended but not required that all patients receive corticosteroid premedication (e.g. Decadron 4 mg p.o. in a single dose, or equivalent) 15-60 minutes prior to each of the five treatments for the intended purpose of modulating immediate acute inflammatory effects. Medicines useful in

general for urinary flow obstruction may be used in cases where prostatic swelling causes urinary outlet obstruction. Analgesic premedication to avoid general discomfort during long treatment durations also is recommended when appropriate.

6.1.4 *Supportive medicines*

Consider Tamsulosin (e.g., Flomax) during treatment period to reduce urinary symptoms. Also consider using 5-alpha reductase inhibitor like Finasteride (e.g. Proscar) to relieve potential obstructive issues.

6.2 Technical Factors

6.2.1 *Physical Factors*

Only photon (x-ray) beams produced by linear accelerators, betatrons, or microtron accelerators with photon energies 6-21 MV will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed.

6.2.1 *Dose Verification at Treatment*

Personal dosimeter measurements (e.g. diode, TLD, etc.) may be obtained for surface dose verification for accessible beams as per institutional preference. This information is not required by the protocol.

6.3 Localization, Simulation, and Immobilization

6.3.1 *Patient Positioning*

Patients will be positioned supine in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients external contours) with reference to the stereotactic coordinate system (see Section 6.1). All positioning systems must be validated and accredited by the Study Committee (Principal Investigator and Institutional PIs) prior to enrolling or treating patients on this trial. Patient immobilization must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%).

6.3.2 *Inhibition of Effects of Internal Organ Motion*

Special considerations must be made to account for the effect of internal organ motion (i.e., breathing, etc.) on target positioning and reproducibility. In some cases, the intrafractional tumor motion is small and no special maneuvers are required to achieve motion limits as defined in section 6.4 (this may be true for many cases of prostate cancer). Treating in the prone position will accentuate internal organ motion problems related to breathing and should be avoided unless special measures are taken to account for this motion. When accounting for intrafractional motion, acceptable maneuvers including reliable abdominal compression, accelerator beam gating with the respiratory cycle, and active breath-holding techniques. Internal organ inhibition maneuvers must be reliable enough to insure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) as defined in Section 6.4 with any significant probability (i.e., < 5%). Assessment of this motion will be left to the institution and may included identifying the position of radio-opaque seeds implanted into the prostate prior to each treatment. This type of interfractional motion analysis with correction is only required by protocol just prior each separate treatment. Intrafraction assessment during the course of each treatment (dynamic and adaptive maneuvers) is allowed and encouraged especially if treatment times are long.

6.3.3 *Localization and treatment maneuvers*

A more direct method of localization of the prostate gland than conventional treatment (i.e., one that uses skin and boney landmarks solely as a surrogate to the prostate position) must be used in this protocol. Acceptable methods would include placing a radio-opaque seed or marker that can be visualized and triangulated using dual imaging or markers that emit a signal that can me used to detect position electronically all placed prior to simulation and planning. Also, it would be acceptable to perform computed tomography such as axial, spiral or conebeam CT prior to each treatment in the treatment position to identify the tumor target directly. Image quality should be good enough to identify the prostate borders.

In addition to the identification of the prostate in the preceding paragraph, the rectum should also be identified and reliably repositioned with a rectal tube. Prior to positioning at least 30 minutes and no more than 2 hours before each treatment, patients should undergo an effective bowel evacuation. Typically, this will involve 1-2 fleet's enemas. This maneuver is to clear the rectum of stool and significant gas accumulation. Just prior to relocalization and treatment, a rectal tube filled with a radio-opaque fluid should be introduced into the rectum to both visualize the rectum and separate the anterior and posterior walls. The rectal balloon and amount of liquid use to fill must be approved by the PI prior to use.

Isocenter port localization films (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit (or patients should undergo a tomographic imaging study utilizing the linear accelerator couch, if available) immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields. Verification CT scans and portal films may be taken at the discretion of the participating institution, but are not required for protocol participation.

6.4 Treatment Planning/Target Volumes

6.4.1 *Image Acquisition*

Computed Tomography (CT) will be the primary image platform for targeting and treatment planning. The planning CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. Treatment planning images should be performed in the treatment position using all aids/maneuvers described above including urethral tube, bladder contrast, urethrogram, and rectal balloon after bowel evacuation with enemas. The treatment planning scans must use a small caliber radio-opaque urethral catheter to allow visualization of the prostatic urethra as it will be a high dose spillage avoidance structure for treatment planning as indicated in section 6.4.2 below. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

Image fusion with other imaging modalities such as MRI that might be useful in delineating the target and normal tissues is encouraged.

The entire prostate without the seminal vesicles will constitute the CTV target for this protocol. It is not required to identify a GTV within the prostate, but if institutions have special techniques to identify the gross tumor, such as MRI with high tesla strength, it is encouraged to collect the contours. CTV target volume (entire prostate gland) will be outlined by an appropriately trained physician. The target will generally be drawn using CT soft tissue windows. An additional 0.3-0.5 cm in the axial plane and 0.5-1.0 cm in the longitudinal plane (cranio-caudal) will be

added to the GTV to constitute the planning treatment volume (PTV) depending on the institution's accuracy and treating physician's preference.

6.4.2 *Dosimetry*

Three-dimensional coplanar or non-coplanar 3-D beam, arc rotation, or Intensity Modulated Radiotherapy (IMRT) beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Typically, 10-15 beams of radiation will be used with roughly equal weighting. Generally, more beams are used for larger lesion sizes. When static beams are used, a minimum of 10 non-opposing beams should be used. For arc rotation techniques, a minimum of 360 degrees (cumulative for all beams) should be utilized. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Field aperture size and shape should correspond nearly identically to the projection of the PTV along a beam's eye view (i.e. no additional "margin" for dose build up at the edges of the blocks or MLC jaws beyond the PTV). As such, prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COM_{PTV}). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COM_{PTV} must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning, typically around 80% but ranging from 60-90%. The prescription dose in five fractions will be delivered to the margin of the PTV and fulfill the requirements below. As such, a "hot spot" will exist within the PTV centrally at the COM_{PTV} with a magnitude of the prescription dose times the reciprocal of the chosen prescription isodose line (i.e., 60-90%).

For purposes of dose planning and calculation of monitor units for actual treatment, all tissues within the body should be modeled in the planning system as to their electron density. Proper heterogeneity correction algorithms should be approved by the PI.

Successful treatment planning will require accomplishment of all of the following criteria:

1) Normalization
   The treatment plan should be normalized such that 100% corresponds to the center of mass of the PTV (COM_{PTV}). This point will typically also correspond (but is not required to correspond) to the isocenter of the treatment beams.
2) Prescription Isodose Surface Coverage
   The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose.
3) Target Dose Heterogeneity

The prescription isodose surface selected in number 2 (above) must be ≥ 60% of the dose at the center of mass of the PTV (COM_{PTV}) and ≤ 90% of the dose at the center of mass of the PTV (COM_{PTV}). The COM_{PTV} corresponds to the normalization point (100%) of the plan as noted in 1) above.

4) High Dose Spillage
   a) *Location*
      Any dose greater than 105% of the prescription dose should occur primarily within the PTV itself and not within the normal tissues outside of the PTV. Therefore, the cumulative volume of all tissue outside of the PTV receiving a dose greater than 105% of prescription dose should be no more than 15% of the PTV volume. *However, if possible, attempts should be made to avoid higher than the prescription isodose to the prostatic urethra within the prostate.* Ideally, these hot spots will be manipulated to occur within the peripheral zones of the prostate. IMRT and other techniques will be encouraged to accomplish this goal.
   b) *Volume*
      Conformality of PTV coverage will be judged such that the ratio of the volume of the prescription isodose meeting criteria 1) through 4) to the volume of the PTV is ideally less than 1.3 .

5) Respect all critical organ dose-volume limits listed in Section 6.5.1 below.
6) Urethral "hot spot" avoidance. It is recommended that efforts be made by the use of compensation or intensity modulation to avoid excessive dose to the urethra. The prostatic urethra should be identified as an avoidance structure such that dose beyond the prescription dose ideally does not fall on this structure. As an example, if the treatment dose covering the PTV corresponds to the 80% isodose line for a given patient, hot spots of 20% higher dose will exist within the prostate. The intensity modulation techniques should be employed to distribute these hot spots away from the prostatic urethra and more into the peripheral zones of the prostate. Part of the rationale for daily image guidance on this protocol is to carry out this intention of avoiding a "hot spot" to the urethra in practice during treatment as depicted on the treatment plan.

6.5 Critical Structures

6.5.1 *Critical Organ Dose-Volume Limits*

The following table lists maximum dose limits to a point or volume within several critical organs. These are absolute limits, and treatment delivery that exceeds these limits will constitute a major protocol violation (See Section 5.7). The dose is listed as total over 5 fractions and per fraction.

These limits were formulated with the approval of the study committee using known tolerance data, radiobiological conversion models, norms used in current practice at academic centers. Participating centers are encouraged to observe prudent treatment planning principles in avoiding unnecessary radiation exposure to critical normal structures irrespective of these limits.

In order to verify each of these limits, the organs must be contoured such that appropriate dose volume histograms can be generated. Instruction for the contouring of these organs will follow below.

Organ	**Volume**	Dose (cGy)
Spinal Cord	Maximum point dose	22.5 Gy (4.5 Gy per fraction)
	Less than 10 cc	20 Gy (4 Gy per fraction)
Cauda Equina	Maximum point dose	27.5 Gy (5.5 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Sacral Plexus	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	27.5 Gy (5.5 Gy per fraction)
Peri-prostatic Anterior rectal wall	Maximum point dose	No more than 105% of prescription dose
Peri-prostatic Lateral rectal walls	Maximum point dose	No more than 100% of the prescription dose
	Less than 3 cc cumulative (both sides)	50 Gy (10 Gy per fraction)
Peri-prostatic Posterior rectal wall	Maximum point dose	20 Gy (4 Gy per fraction)
Rectum superior to prostate	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Small intestine	Maximum point dose	30 Gy (6 Gy per fraction)
	Less than 10 cc	25 Gy (5 Gy per fraction)
Prostatic urethra	Maximum point dose	No more than 105% of prescription dose
Bladder	Maximum point dose	No more than 105% of prescription dose
	Less than 10 cc	20 Gy (4 Gy per fraction)
Penile bulb	Maximum point dose	No more than 105% of prescription dose
	Less than 3 cc	30 Gy (6 Gy per fraction)
Femoral heads	Less than 10 cc cumulative (both sides)	30 Gy (6 Gy per fraction)
Skin within fold (e.g., the gluteal fold)	Maximum point dose	20 Gy (4 Gy per fraction)
Skin not within fold	Maximum point dose	25 Gy (5 Gy per fraction)
Seminal Vesicles	No dose constraint	Collect dose statistics for documentation only

6.5.2 *Contouring of Normal Tissue Structures*

6.5.2.1 Spinal Cord

The spinal cord will be contoured as one structure based on the bony limits of the spinal canal. The spinal cord should be contoured anywhere it is visualized in the treatment plan (typically superior to L2).

6.5.2.2 Cauda Equina

The cauda equina will be contoured as one structure based on the bony limits of the spinal canal. The cauda equina should be contoured starting superiorly at the bottom of the spinal cord (typically around L2 and terminal at the inferior extent of the thecal sac (typically at S3).

6.5.2.3 Sacral Plexus

The left and right sacral plexus will be contoured collectively as one structure. The location of the sacral plexus will be approximated by contouring the space defined medially by the sacral foramina from S1-S3 including contouring within the sacral foramina, posteriorly along the limits of the true pelvis, laterally to 2-3 cm lateral to the sacral foramina, and anteriorly about 3-5 mm from the posterior limits of the countour.

6.5.2.4 Peri-prostatic Rectal wall

The circumference of the rectum adjacent to the prostate will be divided into 4 equal quadrants (anterior, left lateral, right lateral, and posterior). Assigning 0 degrees at the most anterior aspect of the rectum at the mid sagittal plane, the dividing lines between each quadrant will occur at 45, 135, 225, and 315 degrees. The right and left lateral walls will be combined into a single structure. Only the rectal wall will be included in these contours, not the contents of the lumen. Patients will be treated with a rectal balloon filling the lumen which should therefore not be included in the contours.

6.5.2.4.1 *Anterior Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the anterior quadrant of the rectal wall (from 315 to 45 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate.

6.5.2.4.2 *Lateral Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the lateral quadrant of the rectal wall (from 45 to 135 degrees and also from 225 to 315 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate. These two structures should be combined as a single structure for purposes of dose volume analyses.

6.5.2.4.3 *Posterior Peri-prostatic Rectal Wall*

Starting inferiorly just above the anal sphincter, the posterior quadrant of the rectal wall (from 135 to 225 degrees) should be contoured (absent the lumen) up to 1 cm above the superior extent of the prostate.

6.5.2.5 Rectum Superior to Prostate

Starting inferiorly at the superior extent of the Peri-prostatic Rectal Wall described above, the entire wall and lumen of the rectum should be contoured up to the level of the sacral promontory.

6.5.2.6 Small Intestine

The small intestines should be contoured as a conglomerate of all bowel loops within each CT cut starting at the first appearance of small intestine in the pelvis and extending superiorly within each cut.

6.5.2.7 Prostatic Urethra

The prostatic urethra will be identified by the urethral catheter plus 1-2 mm of tissue radially into the prostate. The inferior aspect of the prostatic urethra coincides with the apex of the prostate (urethrograms may be helpful in identifying the apex). The

superior aspect of the prostatic urethra coincides with the base of the prostate at the bladder inlet.

6.5.2.8 Bladder

The bladder should be contoured in its entirety including its contents.

6.5.2.9 Penile Bulb

The penile bulb will be contoured starting superiorly at the inferior aspect of the prostatic urethra and extending inferiorly for 3 cm.

6.5.2.10 Femoral heads

The femoral heads will be contoured bilaterally as one structure.

6.5.2.11 Skin

The skin will constitute the external contour minus 5 mm. The skin within folds, especially in the gluteal folds as the skin surfaces make contact, will be contoured as a separate structure.

6.5.2.12 Seminal vesicles

The seminal vesicles should be contoured right and left as one structure. There is no protocol dose constraint for these structures, but they will be contoured to collect dose deposition data.

6.6 Documentation Requirements

6.6.1 In general, treatment interruptions should be avoided by preventative medical measures and nutritional, psychological, and emotional counseling. Treatment breaks, including indications, must be clearly documented on the treatment record.

6.7 Compliance Criteria

6.7.1 *Accreditation Compliance*

All criteria listed in Section 5 must be completed to the satisfaction of the study committee in order to be accredited. Upon completion of the criteria, a letter will be sent to institutions' PIs informing them of accreditation for the study. No institution will be allowed to enroll patients without accreditation.

6.7.2 *Dosimetry Compliance*

Section 6 describes appropriate conduct for treatment planning dosimetry. Criteria for both major and minor deviations are provided in the table in Section 6.4. In addition to the criteria in section 6.4, the table in Section 6.5 lists dose volume limits for specific organs and structures. Exceeding these limits by more than 2.5% constitutes a minor protocol violation. Exceeding these limits by more than 5% constitutes a major protocol violation.

6.7.3 *Treatment Delivery Compliance*

Set-up films will be compared to digitally reconstructed radiographs from the same beam's eye view. Deviations of less than 0.5 cm in the transverse plane and 1.0 cm in the cranio-caudal plane will be considered compliant. Deviations from 0.5-1.0 cm in the transverse plane and 1.0-1.25 cm in the craniocaudal plane will be considered minor protocol deviations. Deviations greater than those listed as minor will be considered major protocol deviations.

6.8 R.T. Quality Assurance Reviews

Dr. Timmerman will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at the University of Texas Southwestern. Dr. Timmerman will perform the next review after complete data for the next and subsequent 20 cases enrolled has been received at the University of Texas Southwestern. The final cases will be reviewed within 3 months after this study

has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

6.9 Radiation Adverse Events

6.9.1 *Gastro-intestinal*

Monitored treatment related toxicity associated with gastrointestinal function will include colitis, dehydration, diarrhea, enteritis, fistula, nausea, vomiting, obstruction, proctitis, fecal incontinence, stricture/stenosis, hemorrhage, and ulcer. The consequences of gastro-intestinal toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.2 *Renal/Genitourinary/Sexual/Reproductive*

Monitored treatment related toxicity associated with renal and genito-urinary function will include cystitis, fistula, urinary incontinence, urinary obstruction, stricture/stenosis, hemorrhage, and urinary retention. Monitored treatment related toxicity associated with sexual and reproductive function will include erectile dysfunction and ejaculatory dysfunction. The consequences of renal/genitourinary/sexual and reproductive toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE). In addition, patients will fill out the AUA scoring sheets reflecting basic urinary function at regular intervals according to the study calendar in Appendix VI.

6.9.3 *Neurology*

Monitored treatment related toxicity associated with neurology function will include myelitis, motor and sensory neuropathy, plexopathy, and pain. The consequences of neurology toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.4 *Blood/Bone Marrow*

Monitored treatment related toxicity associated with blood and bone marrow function will include anemia, leukocytopenia, thrombocytopenia, and myelodysplasia. The consequences of blood and bone marrow toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.5 *Constitutional Symptoms*

Monitored treatment related toxicity associated with constitutional function will include fatigue, fever, and weight loss. The consequences of constitutional toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.6 *Skin*

Monitored treatment related toxicity associated with skin function will include fibrosis, rash (desquamation), ulceration, and telangiectasia. The consequences of skin toxicity should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE).

6.9.7 *Quality of Life and Other Toxicities*

Other treatment related toxicity attributed to the therapy will be captured, recorded and the consequences of should all be graded according to the Common Terminology Criteria For Adverse Events (CTCAE). Quality of life after prostate cancer treatment will be assess using the Expanded Prostate Cancer Index Composite (EPIC) formalism [41]. Validation and description of this scale can be found at the website:
http://roadrunner.cancer.med.umich.edu/epic/epicmain.html

6.10 Radiation Adverse Event Reporting

6.10.1 AdEERS

AdEERS constitutes a mechanism for reporting serious adverse events to the NCI for reporting purposes. It includes convenient forms for collecting the data. While the forms will not be sent to the NCI for this protocol, we will use the AdEERS forms for data collection of adverse events. Instead of sending the forms to NCI, the participating institutions will send the forms to the University of Texas Dept. of Radiation Oncology Research Office. The address is in section 12.0. AdEERS provides a radiation therapy (RT)-only pathway for events experienced involving RT only. These types of events involving RT only must be reported via the AdEERS RT-only pathway.

The following must be reported via the AdEERS RT-only pathway:

	3		3		4 & 5	4 & 5
	Unexpected		Expected		Unexpected	Expected
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization		
Unrelated Unlikely	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days[1]	10 Calendar Days[1]
Possible Probable Definite	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24 Hour: 5 Calendar Days	10 Calendar Days

Note:
- [1]All grade 4 and 5 adverse events (AEs) that occur during or within 30 days after the completion of radiation therapy (RT), regardless of causation, must be reported within 5 days;
- Grade 4 and 5 AEs that occur in follow up (beyond 30 days after the completion of RT but still within the timeframe of follow up of the patient on study) and that are thought to be probably or definitely related to RT (e.g., radiation-induced spinal cord myelopathy) must be reported within 5 days.

7.0 DRUG THERAPY

Not applicable to this trial.

8.0 SURGERY

8.1 Prostate Rebiopsy

8.1.1 A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality. A PSA failure is defined as a consistent and significant rise in the PSA. The RTOG-ASTRO definition (also known as the Phoenix definition) of PSA failure will be used. Thus, when the PSA rises by more than 2 ng/ml above the lowest level (nadir) achieved after treatment, biochemical failure has occurred and the date of the failure is recorded at the time the nadir plus 2 ng/ml level is reached.

8.1.2 Biopsies are strongly recommended for patients with evidence of distant failure to assist inaccurately determining the "true" local control rate. In the absence of a biopsy, such patients will be considered local failure if their exam is abnormal. If their exam is normal or if they are post orchiectomy they will be censored at the last point in time they were considered locally controlled and considered "inevaluable" for further assessment of local control.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Obstructive flow medicines (alpha blockers) 5 alpha reductase inhibitors)

9.1.2 Antiemetics

9.1.3 Anticoagulants

9.1.4 Antidiarrheals

9.1.5 Analgesics

9.1.6 Hematopoietic Growth Factors
9.1.7 Herbal products
9.1.8 Nutritional supplementation

10.0 TISSUE/SPECIMEN SUBMISSION

10.1 Tissue/Specimen Submission

Serum will be collected on this trial. No specific policy for tumor or normal tissue collection will be outlined for this trial, although it is the intention of the investigators to ideally collect such tissues. Companion protocol(s) have or will be developed to analyze this tissue and blood as part of translational science investigation.

10.2 Specimen Collection For Central Review For Eligibility

Central review of pathology is not required for entry on to this study. However, it is encouraged that diagnostic materials be sent for 2nd review and interpretation especially in difficult cases to ensure consensus in meeting eligibility requirements. This review is not required nor reimbursed as part of the protocol but part of standard of care.

10.3 Specimen Collection for Tissue Banking and Translational Research

Serum will be collected and frozen for subsequent analysis for all patients on this trial.

10.3.1 Serum should be spun from blood collection specimens. It will be stored at a minimum of -20° C prior to shipment.

10.3.2 A Pathology Report from the pretreatment core biopsy describing the original tumor specimen. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.3.3 For serum collection, the following materials must be provided to the Tissue Bank: The Specimen Transmittal Note documenting the date of collection of the serum; the protocol number, the patient's case number, and method of storage (e.g., stored at -20° C).

10.3.4 Submit materials for Tissue Banking, Central Review, Translational Research to:

Michael Story, Ph.D.
UT Southwestern Medical Center at Dallas
5323 Harry Hines Blvd, Dallas, Texas 75390
(214) 648-5557
Michael.story@utsouthwestern.edu

10.4 Reimbursement

Contingent on extramural grant funding, the University of Texas Southwestern will reimburse submitting institutions reasonable compensation per case for fresh or flash frozen tissue; per case for plasma. After confirmation from the The University of Texas Southwestern Radiation Oncology Tissue Bank that appropriate materials have been received, The University of Texas will prepare the proper paperwork and send a check to the institution. Without grant funding, the respective institutions may choose to submit the tissue specimens at their own expense. Patients should not be billed for collection or storage of specimens collected only for the intention of basic and translational research.

10.5 Confidentiality/Storage

10.5.1 Upon receipt, the specimen is labeled with the protocol number and the patient's case number only. The protocol Tissue Bank database only includes the following

information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking and translational research will be stored for an indefinite period of time and may be used for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.6 Translational Research

10.6.1 Rationale

Rationale for translational research will be included in the companion studies protocol(s) approved by the institution's Investigational Review Board (IRB) and the University of Texas Southwestern's IRB.

10.6.2 Specimen Collection

See Section 10.2 for specimen collection requirements.

10.6.3 Specimen Submission

See Section 10.3 for the address information for sending specimens.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix II.

11.2 Follow-up Schedule

11.2.1 Initial follow-up visit at 3 months from start of treatment.

11.2.2 After initial follow-up visit, follow-up will be done at 6, 9, and 12 months post therapy.

11.2.3 Then every six months until five years post-implant.

11.2.4 Then annually thereafter.

11.2.5 A bone scan will be performed on any patient who presents with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.

11.3 Criteria for Toxicity

11.3.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

Please note that this study will not be using separate toxicity scales for acute and late radiation adverse events.

11.4 Measurement of Response

11.4.1 Prostate tumor dimensions in centimeters and grams and PSA values must be recorded on the data collection forms for the initial and follow-up evaluations of the patient.

11.4.2 After study entry, disease evaluations will be made and recorded using the following criteria:

11.4.2.1 No Evidence of Disease (NED): No clinical evidence of disease on digital rectal examination and no PSA failure.

11.4.2.2 Equivocal Disease (ED): This rating will be assigned under the following circumstances:

1) If abnormalities are present on the prostate digital rectal examination but are thought to be abnormal due to treatment and felt not to represent tumor.

2) If clinical evidence of residual tumor is present but this has regressed from a previous examination (initial registration).

3) PSA 2.1 - 4 ng/mL. Rebiopsy is required, before starting hormone therapy, in any patient with PSA failure but with negative bone scan and CT scans. If the biopsy is negative, then they will be scored as NED.

11.4.2.3 Progressive Disease (PD): Progressive disease will be declared if one or more of the following criteria are met:

1) Clinical evidence in the prostate gland of disease progression or recurrence.

2) Clinical or radiographic evidence of tumor recurrence within the pelvic lymphatics or soft tissue beneath the bifurcation of the common iliac arteries,

3) Clinical or radiographic evidence of hematogenous (osseous, hepatic, etc.) and/or extrapelvic lymphatic of soft tissue relapse.

11.5 Other Response Parameters

11.5.1 Disease-Free Interval: The disease-free interval will be measured from the date of accession to the date of documentation of progression or until the date of death (from other causes).

11.5.2 Time to Biochemical Failure: The RTOG-ASTRO definition (also known as the Phoenix definition) of PSA failure will be used. Thus, when the PSA rises by more than 2 ng/ml above the lowest level (nadir) achieved after treatment, biochemical failure has occurred and the date of the failure is recorded at the time the nadir plus 2 ng/ml level is reached.

11.5.3 Time to Local Progression: The time to progression will be measured from the date of study entry to the date of documented local progression as determined by clinical exam.

11.5.4 Time to Distant Failure: The time to distant failure will be measured from the date of study entry to the date of documented regional nodal recurrence or distant disease relapse. Patients with evidence of biochemical failure, but a negative prostate biopsy, will be considered as distant failure only.

11.5.5 Overall Survival: The survival time will be measured from the date of accession to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

11.5.6 Disease-Specific Survival Disease-specific survival will be measured from the date of study entry to the date of death due to prostate cancer. The following will be considered as failure events in assessing disease specific survival:

Death certified as due to prostatic cancer.

Death from other causes with active malignancy (clinical or biochemical progression).

Death due to complications of treatment, irrespective of the status of malignancy.

Death from other causes with previously documented relapse (either clinical or biochemical) but inactive at the time of death will not be considered in disease-specific survival, but will be analyzed separately.

12.0 DATA COLLECTION

Data should be submitted to:

Department of Radiation Oncology
Clinical Research Office
The University of Texas Southwestern Medical Center
Attention: Robbin Paul
5801 Forest Park Road
Dallas, Texas 75390-9183

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission

Item	Due
Demographics	Within 2 weeks of study entry
Eligibility and Entry Characteristics including baseline H&P and PSA	Within 2 weeks of study entry
Pathology Report	Within 2 weeks of study entry
AUA and EPIC baseline forms	Within 2 weeks of study entry
Tissue and serum for translational endpoint (baseline)	Within 2 weeks of study entry
SBRT dosimetry information	Within 1 week after completion of SBRT
Follow-up H&P data including PSA	After last SBRT treatment, post SBRT follow-up at 3, 6, 9, 12 months, then every 6 months to 5 years; then annually thereafter
AUA and EPIC post treatment forms	After last SBRT treatment, post SBRT follow-up at 3, 12, and 24 months
Serum for translational endpoint (post SBRT)	post SBRT follow-up at 3, 12, and 24 months
Adverse Event assessment	After each SBRT treatment, then post SBRT follow-up at 3, 6, 9, and 12 months, then if applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Phase I Study Endpoints

13.1.1 *Primary Endpoint*

The primary endpoint of the phase I portion is to determine the maximum tolerated dose (MTD) by escalating the dose of SBRT toward a tumorcidal dose. Patients will be treated in cohorts of five, followed if necessary by an additional 4 patients. Toxicity will be graded using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) v. 3.0. A dose- limiting toxicity (DLT) is any treatment-related grade 3, 4, or 5 toxicity in the following categories (specific conditions listed in section 6.9): gastrointestinal, renal, genito-urinary, sexual- reproductive, or neurological. A DLT will also include any treatment-related grade 4 or 5 toxicity related in the following categories (specific conditions listed in section 6.9): blood, bone marrow, or constitutional symptoms. In addition, any other grade 4 or 5 toxicity attributed to the therapy constitutes DLT. All reported DLTs will be verified by study chair, data monitoring committee, and independent review before final determination that a DLT has in fact occurred. Doses will be escalated an additional 1 Gy per treatment for 5 treatments (total 5 Gy per increment). The phase I portion of the study will be completed when either of the following events occur: 1) the MTD for a cohort is reached or 2) when sufficiently high dose levels are reached (≥ 13 cy per fraction) to consider the therapy likely to be tumorcidal per determination of the investigators.

13.1.2 *Phase I Dose Escalation*

The phase I study is designed to end if the rate of DLTs within 90 days from the start of treatment exceeds 33%. For each dose level cohorts, a total of 5 patients will be enrolled. If none of these five patients experience a DLT as defined above, then the dose will escalate to the next dose level. If one of these five patients experiences a DLT, then an additional 4 patients will be enrolled. If none of the additional 4 patients experience a DLT, then the dose will escalate to the next level. If two or more patients experience a DLT, then the MTD will

be considered to have been exceeded and will be the next lower dose level. The probability that at least two of nine patients will experience a DLT when the true rate of acute DLTs is 33% is 0.80; that is, the probability of making the correct decision if the true DLT rate is at least 33% is 0.80. The probability that at least two of five patients will experience a DLT when the true rate of acute DLTs is 10% is 0.19; that is, the probability of making the incorrect decision when the true toxicity rate is 10% or less is 0.19.

If very high doses (defined as 12 Gy per fraction or higher) are attained at a level that the investigators feel the therapy should already likely be tumorcidal, the investigators are allowed to proceed to the phase II study for further patient enrollment without actually determining the MTD. The phase II dose will be the last dose level determined to be tolerable for a cohort. If unacceptable rates of in-field tumor progression are observed during the phase II portion, the phase I study may re-open for further patient accrual, but only for dose level(s) which did not previously have two or more DLTs. In such circumstances, untreated patients will be enrolled for further dose escalation starting at the next dose level where the phase I study previously demonstrated tolerable safety.

The sample size of the phase I component of this study will not exceed 54 patients.

13.1.2 *Phase I Waiting Periods*

Dose escalation on the phase I portion of this study should not occur until a sufficient waiting period has occurred after patients have been treated. A period of 90 days must pass in order to assess toxicity. If 90 days have transpired without DLT in the first five (5) patients enrolled to a specific dose level, then dose escalation to the next level may proceed. If one of the first five patients enrolled to a specific dose level experience a DLT, then four additional patients will be enrolled (total nine patients). If 90 days have transpired without toxicity in eight of the nine patients enrolled to that specific dose level, then dose escalation to the next level may proceed.

13.2 Phase II Study Endpoints

Patients will be treated at either the MTD or stopping dose from the phase I study.

13.2.1 *Primary Endpoint*

Late severe GU and GI toxicity is defined as grade 3-5 GU and GI toxicity occurring between 270-540 days (i.e., 9-18 months) from the start of the protocol treatment. It is graded based on CTCAE v3.0. Grade 3-5 GU or GI toxicity that originally occurred prior to 270 days from start of protocol treatment will only be considered late severe GU or GI toxicity if it persists at a severity grade of 3-5 based on CTCAE v3.0 after 270 days.

13.2.2 *Secondary Endpoints*

- Acute severe GU and GI toxicity is defined as grade 3-5 toxicity occurring prior to 270 days from the start of protocol treatment. It is graded based on CTCAE v3.0.
- Non GU and GI toxicity.
- Biochemical failure RTOG-ASTRO definition (also known as Phoenix definition) - Thus, when the PSA rises by more than 2 ng/ml above the lowest level (nadir) achieved after treatment,, biochemical failure has occurred and the date of the failure is recorded at the time the nadir plus 2 ng/ml level is reached.
- Overall survival
- Disease-specific survival
- Clinical progression including local/regional and distant relapse

13.3 Sample Size

13.3.1 *Overview*: The primary goal of this study is to estimate the rate of late grade 3-5 genitourinary and gastrointestinal toxicity following treatment with stereotactic body radiation therapy. For

purposes of this phase II study, late toxicity will be defined as toxicity occurring 270-540 days (i.e, 9-18 months) from the start of radiotherapy. It is graded based on CTCAE v 3.0.

13.3.2 *Sample Size Derivation*: The phase II component of this study is designed to test whether late GU/GI toxicity at 270-540 days from the start of treatment following the protocol treatment is above 10%. The sample size is determined so that the probability of rejecting the treatment because of excessive late toxicity is 90% if the true late toxicity rate is 23% or higher. Assuming an exponential distribution for time from the end of the acute period *(270 days from the start of protocol treatment)* to the occurrence of late toxicity, the hazard rate for the expected 10% toxicity rate and the unacceptable 23% toxicity rate is 0.006/month and 0.015/month, respectively. Following the asymptotic property of the observed hazard and using Z-test for the logarithm of the hazard ratio [35-36], we require 12 cases with severe late GU/GI toxicity. Thus, 47 patients are required to be accrued within three to four years and be followed for 270 days after the acute period (i.e., a total of 540 days) to have a statistical power of 90% with a one-sided significance level of 0.05. Considering 5% ineligible cases and lack-of-data cases, the sample size of the phase II component of this study is 50 patients. Patients treated in phase I at the dose level ultimately used in phase II will be included in the phase II analysis as part of the 50 patient trial.

The sample size of the phase II component of this study will not exceed 50 patients.

13.4 Patient Accrual and Study Duration

13.4.1 It is expected that it will take approximately three to five years to complete the study. The analysis for late toxicity will be carried out after each patient has had at least 270 days (i.e., 9 months) of follow-up from the end of the acute period, a total of 540 days (i.e, 18 months) of follow-up. For the secondary endpoint of biochemical failure, an additional 18 months of follow-up are needed to estimate the 3-year failure rate.

13.5 Analysis Plan

Interim Reports: Interim reports will be prepared every six months until the results of the study is published. In general, the interim reports will contain information about patient accrual rate with projected completion dates of the trial, status of QA review and compliance rate of treatment per protocol, and the frequencies and severity of toxicity.

13.5.2 *The Analysis of Severe Late GU/GI Toxicity*: This analysis will be carried out when each patient has had at least 270 days (i.e., 9 months) of follow-up after the end of the acute period, a total of 540 days (i.e., 18 months) of follow-up. The time to the occurrence of severe late GU/GI toxicity is defined as the time interval from start of protocol treatment to the date of onset of grade 3-5 GU/GI toxicity. The time analysis for recording severe late GU/GI toxicity for this protocol will be limited to 540 days from start of protocol therapy. If no such toxicity is observed before the time of the analysis, the patient will be censored at the time of the analysis. The hazard rate will be estimated by the life table approach with a time span of 18 months. The one-sided Z-test will be used to test the significance of the difference between the logarithm of the observed hazard rate and the logarithm of the hypothesized hazard rate of 0.006/month with variance equal to the reciprocal of the number of cases with late toxicity observed. Because of the lead time of 9 months for the acute period, the 18-month late toxicity will be estimated by the 9-month toxicity rate using the cumulative incidence approach [37] to the defined time to severe late GU/GI toxicity.

13.5.3 *Estimation of Secondary Endpoints Related to the Efficacy*: Cumulative incidence approach [37] will be used to estimate the failure rate for biochemical, disease-specific, local-regional and distant failures. Kaplan-Meier method [38] will used to estimate the overall survival rate.

13.6 Gender and Minorities

Projected Minority Inclusion

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	NA	16	16
Not Hispanic or Latino	NA	88	88
Ethnic Category: Total of all subjects*	NA	**104**	**104**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	NA	2	2
Asian	NA	6	6
Black or African American	NA	19	19
Native Hawaiian or other Pacific Islander	NA	2	2
White	NA	75	75
Racial Category: Total of all subjects*	NA	104	**104**

NA = Not Applicable

14.0 DATA SAFETY MONITORING PLAN

14.1 Data Safety Monitoring Committee and Institutional IRB reporting

A data safety monitoring committee including radiation oncologists not participating in this trial will be formed to review toxicity endpoints and efficacy data. In the phase I component, the data safety monitoring committee will review and verify all reported DLTs. In particular, this committee will scrutinize the grading of adverse events and the attribution to therapy previously assigned by the investigators. This panel will have access to basic patient information so as to have the ability to critically review toxicity events. This study will use this committee to perform ongoing safety assessment at regular defined intervals defined in the statistics section of this protocol. Unexpected toxicities occurring between defined interim analyses points will be reported to the treating center's IRB and also to the University of Texas Southwestern IRB.

14.2 Early Stopping for Toxicity

In phase I, stopping for toxicity will be related to dose limiting toxicity as described in the statistical section. Early stopping of the phase II portion of this protocol will be based on unacceptable toxicity, defined as grade 3 - 5 toxicity related to the following organ systems: gastrointestinal, renal, genitor-urinary, sexual, reproductive, neurological, blood, bone marrow, or constitutional symptoms OR any other grade 4 or 5 toxicity attributed to the therapy occurring in 30% or more of treated patients. If a single patient has more than one unacceptable toxicity, they will only be counted as one unacceptable toxicity for this analysis.

Three interim analyses of toxicity are planned after 25% (12 patients), 50% (24 patients), and 75% (36 patients) of the total number of evaluable patients to be accrued in phase II. These interim analyses will be done after patients have finished their toxicity assessment periods for each group (i.e., 90 days of post therapy follow-up).

The following early stopping rules reject the null hypothesis that the toxicity rate is less than or equal to 10% in favor of the alternative hypothesis that the toxicity rate is at least 30% with an overall Type I error rate of no more than 0.05[5]:

6 or more cases of unacceptable toxicities out of the first 12 evaluable patients, or
7 or more cases of unacceptable toxicities out of the first 24 evaluable patients, or
8 or more cases of unacceptable toxicities out of the first 36 evaluable patients.

The final analysis will test the same null hypothesis using the rejection rule of 10 or more patients with unacceptable toxicities out of the total sample of 47 evaluable patients. This will insure an overall significance level of 0.05 for the final conclusion. If more than 47 of the 50 accrued patients are evaluable, then the first 47 evaluable patients will be used for this analysis.

If the number of unacceptable toxicities observed demonstrate via the monitoring rules above that the treatment-related unacceptable toxicity rate is 30% or more, consideration will be initiated for stopping the study. In this case, the study chair, study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about continuing the study. Additionally, the treatment-related unacceptable toxicity rate will continued to be monitored during the five year follow-up period. If the unacceptable toxicity rate exceeds 30% at any time during the five year follow-up period, the study chair, study PIs, and statistician will review the toxicity data along with the Data Safety Monitoring Committee and make appropriate recommendations about reporting the information.

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APPENDIX I

SAMPLE CONSENT FORM

STUDY TITLE:

PHASE I AND II STUDY OF STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR LOW AND INTERMEDIATE RISK PROSTATE CANCER

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have prostate cancer.

WHY IS THIS STUDY BEING DONE?

There are two separate phases of this study. The first purpose of the first phase is to initially find a potent but reasonably safe dose of a new therapy called stereotactic body radiation therapy (SBRT) for treating prostate cancer. Once this potent but reasonably safe dose is found, the second phase will treat additional patients with SBRT to see what effects (good and bad) it has on prostate cancer. This research is being done because although SBRT is used to treat a variety of cancers, it hasn't been used extensively to treat prostate cancer and needs more investigation.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

Patients will be treated in only one of the phases of the study, not both. Between 5-54 patients will take part in the first phase of the study (depending on their tolerance) and another 50 patients will take part in the second phase. Therefore, a total of between 55-104 patients will participate altogether.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following tests and procedures:

Work-up	**Treatment**	**Follow-up**
Physical Exam PSA Prostate Biopsy Metallic seed implantation CT or MRI Scan	Pre-planning session and Stereotactic Body Radiation Therapy	3 months from start of treatment, then at 6, 9 and 12 months; then every 6 months x 5 years.

During the work-up, your doctor will place 2-3 small metallic markers into your prostate to allow the gland to be visualized using x-rays. This will be

done through the rectum in a manner similar to how the prostate biopsy was performed.

As part of the pre-planning session (simulation) you will undergo several procedures to help make the treatment more accurate.

1. You will give yourself an enema (or two) within an hour or two prior to the planning session and each treatment to clear all the stool and air out of your rectum.
2. The doctors, nurses, or technicians will insert a flexible tube (catheter) into your bladder through the urethra within your penis. They will first empty your bladder and then refill it partially with a special liquid visible to x-rays. This tube will remain in place for the planning session and then be removed immediately afterward.
3. The doctors, nurses, or technicians will insert a tube with a deflated balloon on the end into your rectum. Once in place, the balloon will be inflated with air or water to the size of a chicken egg. This balloon will remain in place for the planning session and each treatment and then be removed immediately afterward.

Stereotactic Body Radiation Therapy (SBRT):
SBRT to the prostate will be given once a day, two to three days a week for two to three weeks. A typical radiation treatment lasts about 60-90 minutes. SBRT will be given on an outpatient basis at your institution.

• Procedures that are part of regular cancer care and may be done even if you do not join the study.

Procedure	Schedule
History and Physical Exam	Prior to study entry and at follow-ups
Tumor Measurements	
PSA Blood Test	
Prostate Biopsy	Prior to study entry and at suspicion of treatment failure
Pelvic CT or MRI Scan	Prior to study entry
Cystoscopy (bladder exam)	As medically Indicated

• Standard procedures being done because you are in this study.

Procedure	Schedule
Metallic marker implantation into the prostate	Once prior to treatment.
Insertion of urethral catheter	For treatment planning
Insertion of rectal balloon	For treatment planning and prior to each treatment
Cystoscopy (bladder exam)	As medically Indicated

• Extra procedures being done because you are in this study:

Procedure	Schedule
Stereotactic Body Radiation	Total of 5 treatments, two to three

Therapy	per week for two to three weeks
Prostate Biopsy for Study Purposes	Only if enrolled on a separate companion study
Blood tests for Study Purposes	At study entry, at three, twelve, and twenty-four months after treatment

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the treatment part of the study for two to three weeks.

Follow up visits with your physician will be scheduled for three months after you start treatment, then every three months for one year, then every six months for five more years, and then annually for the rest of your life.

The researchers may decide to take you off this study if it is in your best medical interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the treatment is stopped, but in some cases side effects can be serious or long-lasting or permanent.

<u>Risks Associated with Placement of Urinary Catheter</u>
Very Likely
Pain or discomfort during insertion

Less Likely, But Serious
Bleeding from the urethra or bladder
Urethral irritation with urge to frequently urinate
Urinary tract infection (UTI)

<u>Risks Associated with Stereotactic Body Radiation Therapy</u>
Very Likely
Tanning or redness of skin in treatment area
Rash, itching or peeling of skin
Temporary hair loss in the treatment area
Temporary fatigue, nausea or diarrhea
Abdominal cramps
Impotence (may not be reversible)
Rectal irritation with frequent urge to have a bowel movement
Bladder irritation with frequent urge to urinate
Bowel Movements with Mucous

Burning on urination
Injury to urethra slowing causing a narrowing (may need surgical correction)

Less Likely, But Serious
Injury to the bladder, urethra, bowel or other tissues in the pelvis or abdomen
Rectal bleeding, intestinal or urinary obstruction, and ejaculatory dysfunction (may not be reversible)

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. The treatment may cause sterility, however, adequate birth control measures must still be used. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant while you are on this study, you must tell your doctor immediately.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) convention radiation therapy; (2) hormone therapy; (3) surgery; (4) brachytherapy implant; or (5) no treatment except medications to make you feel better. With the latter choice, your tumor may continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in an computer file at the study headquarters (University of Texas Southwestern in Dallas, TX). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the study coordinators and their designees and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You or your insurance company will not be charged for the prostate biopsies and blood tests done specifically for study purposes. If you are erroneously billed for these specific tests, please contact your study coordinator.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

For information about your disease and research-related injury, you may contact:

_____ _____
Name Telephone Number

For information about this study, you may contact:

_____ _____
Name Telephone Number

For information about your rights as a research subject, you may contact:
(This person should not be the investigator or anyone else directly involved with the research)

_____ _____
Name Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1–800–4–CANCER (1–800–422–6237)** or **TTY: 1–800–332–8615.**

Visit the NCI's Web sites for comprehensive clinical trials information at **www.cancer.gov/clinicaltrials** or for accurate cancer information including PDQ (Physician Data Query) visit **www.cancer.gov/cancerinfo/pdq**

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

_____	_____	_____
Patient's Name	Signature	Date

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

APPENDIX II

STUDY PARAMETER TABLE

	Pre-Treatment		During Treatment		Follow-Up (months after therapy)												
	Within 90 days of study entry	Within 30 days of study entry	With each treatment	After last treatment	3	6	9	12	18	24	30	36	42	48	54	60	Every 12 months after 5 years
Prostate Biopsy with Gleason Score for Diagnosis	X																
PSA		X[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
History/physical		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status		X			X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI of pelvis	X		X[b]														
AUA Symptom index		X		X	X			X		X							
EPIC Questionnaire		X		X	X			X		X							
BUN, creatinine, CBC, & platelets	X[c]																
Serum for Translational Endpoints		X			X			X		X							
Informed consent		X															
Tumor response evaluation		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Bone scan[D]																	
Adverse event evaluation			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a]Baseline PSA should be recorded as pre-hormonal level if taking hormones even if >30 days prior to entry.
[b]CT or MRI prior to each treatment may include conebeam CT
[c]For reference but not eligibility
[d]At time of PSA failure or suspected progression

APPENDIX III

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).**
2	**Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).**
5	**Death (Karnofsky 0).**

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX IV

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

DEFINITION OF TNM

Primary Tumor, Clinical (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically inapparent tumor neither palpable or visible by imaging
- T1a Tumor incidental histologic finding in 5% or less of tissue resected
- T1b Tumor incidental histologic finding in more than 5% of tissue resected
- T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)\

T2 Tumor confined with prostate*
- T2a Tumor involves one-half of one lobe or less
- T2b Tumor involves more than one-half of one lobe but not both lobes
- T2c Tumor involves both lobes

T3 Tumor extends through prostate capsule**
- T3a Extracapsular extension (unilateral or bilateral)
- T3b Tumor involves the seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall.

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

Primary Tumor, Pathologic (pT)

pT2* Organ confined
- pT2a Unilateral, involving one-half of one lobe or less
- pT2b Unilateral, involving more than one-half of one lobe but not both lobes
- pT2c Bilateral disease

pT3 Extraprostatic extension
- pT3a Extraprostatic extension**
- pT3b Seminal vesicle invasion
- pT4 Invasion of bladder, rectum

*Note: There is no pathologic T1 classification
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

APPENDIX IV (continued)

AJCC STAGING SYSTEM
PROSTATE, 6th Edition

Distant Metastasis (M)*

MX	Presence of distant metastasis cannot be assessed (not evaluated by any modality)	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used; pM1c is most advanced.

Histopathologic Grade (G)

GX	Grade cannot be assessed
G1	Well-differentiated (slight anaplasia [Gleason 2-4])
G2	Moderately differentiated (moderate anaplasia [Gleason 5-6])
G3-4	Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

Stage Grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	N0	M0	G2, G3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

APPENDIX V

GLEASON CLASSIFICATION

Histologic patterns of adenocarcinoma of the prostate

Pattern	Margins Tumor Areas	Gland Pattern	Gland Size	Gland Distribution	Stromal Invasion
1	Well defined	Single, separate, round	Medium	Closely packed	Minimal, expansile
2	Less definite	Single, separate rounded but more variable	Medium	Spaced up to one gland diameter, average	Mild, in larger stromal planes
3	Poorly defined	Single, separate more irregular	Small, medium, or large	Spaced more than one gland diameter, rarely packed	Moderate, in larger or smaller stromal planes
or 3	Poorly defined	Rounded masses of cribriform or papillary epithelium	Medium or large	Rounded masses with smooth sharp edges	Expansile masses
4	Ragged, infiltrating	Fused glandular masses or "hypernephroid"	Small	Fused in ragged masses	Marked, through smaller planes
5	Ragged, infiltrating	Almost absent, few tiny glands or signet ring	Small	Ragged anaplastic masses of epithelium	Severe between stromal fibers or destructive
or 5	Poorly defined	Few small lumina in rounded masses of solid epithelium central necrosis	Small	Rounded masses and cords with smooth sharp edges	Expansile masses

The Gleason Classification is a system of histologic grading based on over-all pattern of tumor growth at relatively low-magnification *(40 to 100x)*. Five patterns of growth are recognized and numbered in order of increasing malignancy. Because of histologic variation in the tumor, two patterns are recorded for each case, a primary or predominate pattern and a secondary or lesser pattern.

The Gleason Score is the sum of the primary and secondary pattern, If only one pattern is present, the primary
and secondary pattern receive the same designation.

(Primary = 2, Secondary = 1, Gleason = 3)
(Primary = 2. Secondary = 2, Gleason = 4)

1. Gleason, D.F. et al: Prediction of prognosis for prostatic carcinoma by combined histologic grading and clinical staging. J Urol 111:58, 1974.

APPENDIX VI

ON-STUDY AUA SYMPTOM SCORE (PQ)

PATIENT NAME _____ CASE # _____

INSTITUTION NAME _____ TOTAL SCORE _____

PLEASE FILL OUT THIS SHORT QUESTIONNAIRE TO HELP US FIND OUT MORE ABOUT ANY URINARY PROBLEMS YOU MIGHT HAVE. CIRCLE A NUMBER IN EACH COLUMN THAT BEST DESCRIBES YOUR SITUATION. YOU MUST ANSWER ALL QUESTIONS.

	Not at all	**Less than one time in five**	**Less than half the time**	**About half the time**	**More than Half the time**	**Almost always**
1. Over the past month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
2. Over the past month or so, how often have you had to urinate again, less than two hours after you finished urinating?	**0**	**1**	**2**	**3**	**4**	**5**
3. Over the past month or so, how often have you found you stopped and started again several times when you urinated?	**0**	**1**	**2**	**3**	**4**	**5**
4. How often do you find it difficult to postpone urination?	**0**	**1**	**2**	**3**	**4**	**5**
5. Over the past month or so, how often have you had a weak urinary stream?	**0**	**1**	**2**	**3**	**4**	**5**
6. Over the past month or so, how often have you had to push or strain to begin urination?	**0**	**1**	**2**	**3**	**4**	**5**
	Not at all	**Once every 8 hours**	**Once every 4 hours**	**Once every 3 hours**	**Once every 2 hours**	**At least once every hour**
7. Over the past month or so, how often did you most typically get up at night to urinate?	**0**	**1**	**2**	**3**	**4**	**5**

Total per column _____ _____ _____ _____ _____

_____ _____

Patient Signature Date This Form was Completed

APPENDIX VII

EXPANDED PROSTATE CANCER INDEX COMPOSITE (EPIC)

Quality of life after prostate cancer treatment will be assessed using the Expanded Prostate Cancer Index Composite (EPIC) formalism [41]. Validation and description of this scale can be found at the website: http://roadrunner.cancer.med.umich.edu/epic/epicmain.html

The actual forms used for this assessment can also be downloaded on a PDF file from this website. We will use the standard form for this protocol.

Hypoxia Assessment in Localized Prostate Cancer:
A Companion Protocol to a Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

University of Texas Southwestern Medical Center

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Department of Radiology

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Schema

STUDIES UTILIZED

Tumor hypoxia assessments	**1.) Blood Oxygen Level Dependant (BOLD) Magnetic Resonance Imaging (MRI) enhancement and** **2.) Assessment of deposition of pimonidazole in prostate tissue. This involves intravenous administration of the drug with subsequent core biopsies of the prostate**

TIMING OF STUDIES

The studies listed above will be carried out 1-3 weeks prior to the start of Stereotactic Body Radiation Therapy (SBRT) done on the Phase I/II trial

ELIGIBILITY

Patients consented, eligible, and scheduled to be treated on the phase I/II study of SBRT for localized prostate cancer.

INELIGIBILITY

Patients with contraindications to functional imaging and pimonidazole(e.g. allergy to agent used in studies).
Patients with significant bleeding disorder for which prostate biopsy is contraindicated.
Patient unwilling to fulfill requirements of both protocols.

1.0 BACKGROUND & RATIONALE

1.1 Clinical Protocol

Prostate cancer has several good treatment options for organ confined disease such as surgery and conventional radiation. In addition, some men with indolent disease are appropriately treated with watchful waiting. However, all of the established treatments continue to fail in a portion of patients via tumor recurrence. Furthermore, current treatments are often unpalatable for many patients because they are either too invasive or too inconvenient. It has also been shown recently that many prostate cancers may be better controlled using large dose per fraction treatments such as might be delivered by stereotactic body radiation therapy (SBRT). While large dose per fraction treatments are facilitated by new generation radiation delivery equipment, technology cannot independently overcome normal tissue consequences to tubular organs adjacent or within targets (e.g., the urethra and rectum for prostate cancer). As such, careful prospective clinical trials must be designed that appropriately bridge the information learned from laboratory testing, historical clinical experience, and the clinical experience with SBRT from other sites in order to test this new therapy for prostate cancer. This is an important problem, since localized prostate continues to recur despite current treatments and more effective, less toxic and more convenient treatments are necessary.

As the SBRT therapy is strictly local, we will select for patients with prostate cancer locally confined to the prostate gland. As such, we will select eligibility criteria sanctioned in the past by the Radiation Therapy Oncology Group to predict a reasonably low risks of both extraprostatic capsular extension and seminal vesicle invasion. We will apply the Roach formula to limit eligibility to patients with under a 20% risk of pelvic lymph node involvement. Some patient eligible for this trial may have a somewhat higher risk of extraprostatic spread (e.g, T2b, Gleason 7 or PSA>10) and it will be allowed to use pre-treatment hormonal therapy in such patients at the investigator's discretion. Hormonal therapy may also be used to shrink prostates that are massively enlarged. As the primary toxicity will likely be mucosal damage, we will avoid enrolling patients with pre-existing mucosal dysfunction (including those with previous radiation, TURP, very large prostate glands, and inflammatory bowel disease). In this way, patients will be uniformly selected in a fashion that would identify patients likely to receive benefit from the therapy.

As the most efficacious SBRT dose for treatment of the prostate has not been prospectively identified, we will start with a careful phase I dose escalation toxicity study. Patients enrolled at each dose level will undergo routine evaluations to identify potential toxicities. Adequate waiting periods will be respected to insure dose escalation does not proceed prior to observing toxicity. When the MTD is determined or the dose reaches a significantly high level expected to be both tumoricidal and able to control PSA by the investigators, subsequently enrolled patients will be accrued into the phase II portion. In the phase II portion, further patients will be accrued to confirm toxicity data on a larger scale, and attempt to characterize whether there is enough beneficial effect in this population to warrant further clinical testing.

We will use a treatment regimen carried out in 5 total fractions. This would be a more tolerant regimen than our 3 fraction regimens published in liver and lung cancer [1-2] and may lessen the toxicity to serial functioning tissues in close approximation to the prostate (rectum and urethra).

Given there will be only 5 treatments, daily enemas, rectal tubes, and even urethral catheters are all feasible undertakings that may help optimize the therapy.

It is predicted that the dose limiting toxicity from this treatment will likely relate to urethral dysfunction (e.g., ulceration, bleeding, pain, narrowing and frank stricture) and rectal damage (ulceration, bleeding, chronic inflammation, and pain). Since the radiotherapy target for radiotherapy of the prostate is the entire gland, the urethra will by definition be situated toward the center of the target thereby receiving the target margin dose at a minimum. In fact, the urethra may receive even a higher dose than the minimum target dose owing to the fact that SBRT dosimetry commonly includes a 10-30 percent higher central dose within the target. While wedges and other methods of modulation (including IMRT) may be used to steer this higher dose away from the visualized urethra, these techniques will have limited ability to protect the urethra. The prostatic urethra will likely be significantly damaged which may limit dose escalation. If it has the ability to heal by second intention as it has been shown to do after other severe insults such as transurethral resection without forming a diffuse untreatable stricture, the treatment may still be feasible. Certainly if mucosal clonagens can migrate from the bulbous urethra and bladder to "rescue" the prostatic urethra after SBRT, care will be taken to spare dose to those structures [3]. In regard to the rectum, the treatments will be carried out with a rectal tube to separate much of the circumference of the rectal wall from the prostate target. This rectal tube must be positioned appropriately above the anus and extend superiorly to above the prostate to be effective. In addition, the rectum should be evacuated of feces to avoid confounding the geometry prior to each treatment. If the dose to the rectum is tightly confined to the anterior wall next to the target, it is hoped that the ulcer likely to be produced will heal by recruitment of clonagens and blood supply from the lateral and posterior walls. Indeed, a precedent for assuming such a process exists with the reported treatment of small rectal cancers using an endorectal orthovoltage tube by Papillon and colleagues [4]. In that experience, doses as high as 150 Gy were given in as few as 4 fractions which undoubtedly resulted in ulceration at the point of treatment but still no reported long term untoward toxicity owing to the extremely localized high dose dosimetry.

1.2 Companion Protocol

One of the most recognized tumor/host factors that may lead to radioresistance is hypoxia. Hypoxic cells may have more radiation resistance than well oxygenated cells. Hypoxic cells are associated with genetic instability, angiogenesis, and metastases [5]. Damage from radiation occurring in a hypoxic tumor is less likely to be permanent. Hypoxic tumors were historically identified as those that undergo central necrosis, such as large lung cancers and malignant gliomas. More recently, though, it has been recognized that hypoxia cannot be assessed only on imaging studies. Indeed, investigators have found that hypoxia exists within human prostate cancers as measured by sophisticated probes, and that treatment failure is more likely than with well oxygenated circumstances [6-10].

The goal of this protocol is to examine tumor oxygenation non-invasively. Many techniques have been developed to examine tumor oxygenation and hypoxia including hypoxia reporter

agents, polarographic electrodes, fiber optic probes, NIR spectroscopy, and various NMR techniques [11-16]. Some of these techniques are invasive. Others lack spatial resolution or lack the ability to dynamically quantitatively sample the response to intervention. Some do not actually measure oxygen tension, rather, surrogates of hypoxia. While we have experience with several methods, this companion protocol will focus on two. First, as a measure of profound hypoxia, we will perform pimonidazole infusion in consenting patients prior to biopsy. Pimonidazole only forms adducts with proteins in those cells that have oxygen concentrations less than 14 micromolar which is equivalent to a pO_2 of 10 mm Hg at 37^{o}C [17-20]. Multiple biopsies taken after pimonidazole infusion can be processed to indicate a map of hypoxia within a given patients prostate. Second, we will carry out *BOLD* (Blood Oxygen Level Dependent) contrast proton NMR assessment [21-22]. BOLD MRI is sensitive to changes in tumor vascular oxygenation in response to changes in blood oxygen tension. Patients will have NMR (MRI) assessment before and after breathing high concentration oxygen by mask. We have institutional data in breast cancer (personal communication with Debu Tripathy, M.D.) that poor response to BOLD predicts poor response to chemotherapy and may be a marker of tumors likely to need more directed therapies.

For this companion protocol, we intend to make an assessment of both oxygen status and dynamic changes with indroduction of high levels of inspired oxygen. Patients undergoing the correlative investigation will be a subset of the patients already enrolled on the phase I/II study. The subset will include 20 patients offered the protocol consecutively after being identified as eligible for the clinical protocol and separately consented for additional testing. Enrollment of patients on the correlative component will be on a voluntary basis but all patients eligible will be offered the companion protocol.

2.0 OBJECTIVE(S)

2.1 To characterize the status of global hypoxia within the prostate prior to SBRT.

2.2 To quantify the volume of tissue in the prostate biopsy specimens that have pO2 less than 10 mm Hg by using the Pimonidazole staining.

2.3 To assess the volume of prostate initially with low oxygen concentration that becomes re-oxygenated with increased inspired oxygen by using the BOLD methodology with MRI.

2.4 A secondary objective is to collect and store tissue/blood specimens for future molecular analysis for this population of patients treated with SBRT

3.0 ELIGIBILITY CRITERIA

3.1 Patients consented, eligible, and scheduled to be treated on the phase I/II study of SBRT for localized prostate cancer.

3.2 Patients with contraindications to functional imaging or pimonidazole infusion (e.g. allergy to agent used in studies) are ineligible. Patients with significant bleeding disorder for which prostate biopsy is contraindicated are ineligible. Patient unwilling to fulfill requirements of both protocols are ineligible.

4.0 PATIENT REGISTRATION

To register a patient, an investigator will call Robbin Paul at the University of Texas Southwestern Medical Center Department of Radiation Oncology Research Office at 214-648-5542 (beeper 214-822-0032). She will review the eligibility checklist, confirm eligibility, and perform registration of the patient.

5.0 TREATMENT PLAN

BOLD Assessment

Each patient will have an MRI examination within 1-3 weeks prior to the start of SBRT, as outlined on Table 1. Patients will be evaluated using a 1.5 Tesla system (Philips Medical systems) with a rectal or pelvic coil. The technique and specific parameters that will be used are described below: A pulse oximeter will be placed on the toe or finger to monitor arterial oxygen saturation and heart rate. A facemask will be applied to deliver air or oxygen (14 dm^3/min) for the BOLD studies. The mask itself will be applied prior to any imaging, to ensure co-registration without patients being moved out and back into the magnet.

Exam:

1. Explanation of exam including method of breathing of oxygen and patient preparation – (approx. 15 min)

2. Scout and SENSE reference scanning (3 min)

3. Sagittal spin echo (SE), 4 mm T1-weighted (TR/TE = <500 ms/<20 ms), Field of View (FOV) = <20 cm, matrix = >128X256, number of signals averaged (NSA) = 1 or 2. (2 min)

4. Transaxial turbo spin echo (TSE), 4 mm T2-weighted (TR/TE = >2000 ms/>80 ms), FOV = 18-20 cm, matrix = 192X256, NSA = 2. (2 min)

5. Sagittal T2-weighted Fat-Saturated 4 mm sequence (same parameters). (3 min)

6. Sagittal BOLD-sensitive Echo Planar Image (EPI) 5 mm image series prior to, during, and immediately following 8 min session breathing 100% oxygen via a ventilator mask. (15 min).

7. DCE: Sagittal 3D Gradient Echo (GE) 2 mm Fat-Saturated T1-weighted (TR/TE= <40 ms/<10 ms), FOV =<20 cm, matrix = >128X256, NSA = 1, Dynamic image series with temporal resolution of ~1.5 min X 6 – immediately prior to and following intravenous. Gadolinium contrast injection using a power injector (0.1 mM/Kg as a 10-second bolus, followed by a 20 ml saline flush). (10 min)

8. Transaxial TSE 6 mm T2-weighted sectioning through the axilla and chest wall with FOV=~26 cm to assess for lymphadenopathy. (2 min)

Table 2 Imaging Techniques, Measures, and Examination Times

IMAGE METHOD	TECHNIQUE	MEASUREMENT	CONTRAST AGENT	EXAM TIME	COMMENT

MRI-BOLD	Oxygen Uptake Differences	Signal change rate and ratio	Oxygen	15 min	Vascular oxygenation
MRI-Diffusion	EPI; b-values = 0, 300, & 800	Apparent Diffusion Coefficient (ADC)	None	4 min	Sensitivity to necrosis
MRI	Standard contrast enhanced	Contrast	Gadolinium	20 min	Moderate sensitivity to perfusion
MRI-DCE	Dynamic contrast	Perfusion- kTrans Signal change rate and ratio	Gadolinium	8 min	Perfusion and surface permeability

The degree of lesion contrast enhancement will be quantified via direct comparison of pre and post-contrast images of the dynamic scan series and using lesion-to-muscle ratios of pre & post contrast images. A graph of the six temporal data points will be produced and assessed to determine whether the lesion has a washout, plateau, or progressive pattern. Whenever the lesion is large enough (>1 cm) separate signal enhancement regions of interest (ROI) will be obtained for the central and peripheral portions of the tumor as the degree of vascularity of these areas is often different. The time and amplitude of maximal enhancement is used in the assessment. Any significant decrease in tumor vascularity/perfusion will result in a decrease in contrast enhancement and frequently produce a temporal change in the enhancement patterns. The degree of change in the BOLD response of the tumor is determined using simple percentage signal change following oxygen administration. We will also examine the rates of response during the transition to breathing oxygen and the return to air. Diffusion images are used to create apparent diffusion coefficient (ADC) maps that will be evaluated to determine if perfusion and "bound" water within the tumor are altered by therapy. The images obtained with small b-values (200 in our study) are more affected by intravascular perfusion motion than are larger b-value (800) acquisitions. . Each parameter will be assessed on a voxel by voxel basis providing histograms of % changes and rates of response. Analysis of variance (ANOVA) will be used to seek correlated variables and to determine which parameters provide significant insight into the effects of therapy and which change during tumor regression or regrowth of recurrent tumor.

Tissue Studies

A total of 8 core biopsies will be obtained using a core needle and all placed in liquid nitrogen. One hour prior to biopsies, pimonidazole hydrochloride (IND # 36,783, obtained through Drs. James Raleigh and Mahesh Varia at the University of North Carolina) at a dose 500 mg/m^2 added to 100 mL of 0.9% saline will be given intravenously over a period of 20 minutes. Frozen cores will be cryosectioned into 4 µm sections, thawed and fixed in cold acetone (4°C) for 10 minutes, then rinsed and incubated overnight at 4°C with mouse monoclonal anti-pimonidazole antibody (clone 4.3.11.3) diluted 1:10 in PBS containing 0.1% bovine serum albumin c and 0.1% Tween 20. The sections will be incubated for 90 min with Cy-3-conjugated goat anti-mouse

antibody 1:150 (Jackson Immuno Research Laboratories). Between all steps of the staining procedure, the sections are rinsed three times for 2 minutes in PBS. Results will be expressed as % of tumor cells staining and a parallel section stained with H&E will be used as reference for tumor cells.

6.0 TOXICITIES TO BE MONITORED/DOSAGE MODIFICATIONS

Biopsies may be associated with bleeding, infection or hematoma formation. They should be graded according to the Common Toxicity Criteria from the NIH.

Allergies to any agent will be graded in severity. Premedication with antihistimines, anti-inflammatory agents, or steroids may be considered for future scans for mild allergic reactions. More severe allergic reactions or allergies not responsive to premedications constitute an off-study indication. If other severe toxicity resulting in withholding therapy is encountered, the details will be documented.

7.0 STUDY PARAMETERS/CALENDAR

Companion Study of Functional Imaging of
Treatment Effects of Extracranial Stereotactic Radioablation

Required Studies	Pre Treatment*	Post Treatment
Phase I/II Protocol required studies	X	X
Infusion of Pimonidazole followed by core biopsies of prostate	X	
BOLD MRI with oxygen challenge	X	

* carried out no more than 3 weeks and no less than 1 week of first SBRT treatment

8.0 CRITERIA FOR EVALUATION/REMOVAL FROM STUDY

8.1 Definitions related to disease (ie, measurable disease, response, and progression, or relapse).

Criteria outlined in the phase I/II clinical protocol will be utilized.

8.2 Criteria for removal from study.

The following are criteria for discontinuing this companion protocol's studies: a) excessive, life threatening toxicity, b) refusal to complete all planned therapy. All patients will be assessed and evaluated for toxicity if they have received any protocol therapy. Patients who experience significant toxicity will be followed for outcome regardless of whether they successfully completed all planned therapies. Criteria for taking a patient off study include: a) death, b) lost to follow-up, and c) significant allergic reaction.

9.0 DRUG INFORMATION

The BOLD protocol does not involve any investigational drug. Pimonidazole hydrochloride (IND # 36,783, obtained through Drs. James Raleigh and Mahesh Varia at the University of North Carolina through in investigator-held IND [Timmerman] crossfiling Dr. Varia's IND. Pimonidazole does not have any reported serious toxicity, but effects will be monitored. A complete investigators brochure is available.

10.0 STATISTICAL CONSIDERATIONS

Statistical considerations for the sample size for the phase I/II clinical protocol is outlined in the statistical section of that protocol. This companion protocol is an observational study of 20 of the patients on the phase I/II protocol. This sample size was not selected based on a statistical power calculation. Rather, it was chosen to be enough patients to observe variations among patients with regard to the stated objectives and stay within a reasonable budget to pay for the studies offered through a grant. As such, strict quantitative conclusions about measured parameters observed in this study cannot be made. However, for the purposes of the objectives of this study, the sample size should be adequate to make qualitative and semi-quantitative conclusions. The patients will be selected by offering the protocol to each patient enrolled on the phase I/II study in a sequential fashion. Enrollment on this study is on a voluntary basis. There is no requirement of patients to be on both studies. This study will close after enrollment of the sample size of around 20 patients.

11.0 DATA FORMS AND SUBMISSION SCHEDULE

Protocol records for each patient indicating the following will be required for data management of this protocol and kept on file in the Research Office in the Department of Radiation Oncology:

12.0 SPECIAL INSTRUCTIONS

Not applicable to this protocol.

13.0 PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Research Office) and are subject to FDA inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

14.0 REPORTING ADVERSE EVENTS

An adverse event is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the protocol treatment, or it has worsened in intensity or frequency following exposure to the protocol treatment. Adverse events will be graded according to the NCI Common Toxicity Criteria.

Any adverse experience associated with the use of the protocol treatment (possibly, probably, or definitely) that is both serious and unexpected must be reported to the Institutional Review Board within 3 working days after the incident, using the appropriate IRB Adverse Event Form. This form includes the applicable study number and title, and contains the following:

- Assessment of the report and the significance / relevance to the study, e.g., change in risk / benefit ratio
- Statement as to whether the informed consent statement should reflect changes in the potential risks involved
- Statement as to whether this adverse event has been reported previously, and if so, whether the frequency is considered unusually high

DEFINITIONS: The following terms are defined in Food and Drug Administration, HHS 21 CFR 312.32:

"*Associated with the use of the drug*" means that there is a reasonable possibility that the experience may have been caused by the drug.

"*Serious adverse experience*" means any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

"*Unexpected adverse experience*" means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

"*Life-threatening*" means that the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form, might have caused death.

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To: Robert Timmerman, MD
c/o Robbin Paul
Radiation Oncology - 9183

FROM: **Robert Bash, MD**
Institutional Review Board 2 Chairperson
IRB – 8843

DATE: **July 11, 2006**

RE: Final Approval of the Protocol Dated June 1, 2006, NR1, Consent Form, and Acknowledgment of HIPAA Authorization and Spanish Short Consent Form

IRB Number: 062006-010

Title: Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

Thank you for responding to the stipulations as requested by the Institutional Review Board in the memo dated June 29, 2006. This letter is a notification of final approval of the protocol, and attached informed consent document(s) dated July 11, 2006. IRB approval of this research lasts until June 25, 2007. If the research continues beyond twelve months, you must apply for updated approval of the protocol and informed consent document(s) one month before the date of expiration noted above.

Please Carefully Read Important Compliance Information Below:

Your approved number of evaluable subjects is 97. If during the course of your study you feel that you need to change this number, you must submit a completed MOD Form applying for prospective approval to do so.

All subjects must sign a copy of the attached IRB-approved and stamped consent form(s) and HIPAA Authorization, if applicable, before undergoing any study procedures, including screening procedures that would not otherwise be performed for a patient/subject's medical condition in a non-research context.

The above referenced study is approved to enroll Spanish-speaking subjects. DHHS regulations permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally. A witness to the oral presentation is required, and the subject must be given copies of the short form document and the summary.

When this procedure is used with subjects who do not speak or read English, (1) the oral presentation and the short form written document should be in a language understandable to

the subject; (2) the IRB-approved English language informed consent document may serve as the summary; and (3) the witness should be fluent in both English and the language of the subject.

At the time of consent, (1) the short form document should be signed by the subject (or the subject's legally authorized representative); (2) the summary (i.e., the English language informed consent document) should be signed by the person obtaining consent as authorized under the protocol; and (3) the short form document and the summary should be signed by the witness. When the person obtaining consent is assisted by a translator, the translator may serve as the witness.

For research involving therapeutic or prophylactic interventions or invasive diagnostic procedures, a bilingual translator must be continuously available to facilitate communications between research personnel and a subject. If a bilingual translator will not always be available, it may be unsafe for an otherwise eligible candidate to participate in the research if that person does not speak and read English.

Important Note: You must use a photocopy of the attached IRB-stamped consent form(s). Use of a copy of any consent form on which the IRB- stamped approval and expiration dates are replaced by typescript or handwriting is prohibited**.**

A photocopy of the signed consent form(s) and HIPAA Authorization should be given to each participant. The copy of the consent form(s) bearing original signatures should be kept with other records of this research for at least five years past the completion of the study. For research involving treatment or invasive procedures, a photocopy of the signed consent form(s) should be on file in a subject's medical record.

The Department of Health and Human Services (DHHS) regulations for the protection of human subjects require that informed consent information be presented in a language understandable to the subject(s), and, in most situations, that informed consent be documented in writing.

Where informed consent is documented, the written consent document(s) should embody, in language understandable to the subject, all of the elements necessary for legally effective informed consent. Potential subjects who do not speak or read English should be presented with a consent document written in a language understandable to them. The Office for Human Research Protections (OHRP) strongly encourages the use of this procedure whenever possible.

In the future, should you require a change or need to modify the research, including the informed consent document(s) and HIPAA Authorization, per federal regulation you must obtain prospective review and approval of the Institutional Review Board. For any change to the research, prior review and approval before implementing such changes is mandatory except when prompt implementation is necessary to eliminate apparent immediate hazard to a subject.

Approval by the appropriate authority at a collaborating facility is required before subjects may be enrolled on this study.

If you have any questions related to this approval or IRB policies and procedures, you may telephone Kim Batchelor at 214-648-8430.

Attachment(s):NR1
Consent Form
Spanish Consent Form
HIPAA Authorization Form
Spanish HIPAA Authorization Form

RB/kb

IMPACT STATEMENT

Phase I and II Study of Stereotactic Body Radiation Therapy (SBRT) for Low and Intermediate Risk Prostate Cancer

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There are several very good treatments for localized prostate cancer. These include surgical removal (e.g., nerve sparing prostatectomy), external beam radiotherapy (e.g., intensity modulated radiation therapy, IMRT), and both low dose rate and high dose rate brachytherapy implants. Still, many men with prostate cancer find these options are not ideal either due to the invasiveness of the treatments, hospitalizations, or inconvenience. Stereotactic Body Radiation Therapy (SBRT), is a non-invasive therapy generally carried out in 1-5 outpatient treatments. Our group has been active in translating this new treatment paradigm via prospective clinical testing in other extracranial sites including the liver, lung, and kidney. It has already been shown to be extremely effective at eradicating cancer even in many cases where radiation therapy was considered only modestly effective. This is a biologically distinct therapy from conventionally fractionated radiation therapy, and there are strong biological incentives to use the therapy in prostate cancer. Still, there are unique anatomical and functional relationships of the surrounding normal tissues in the pelvis that will make use of this therapy in prostate cancer potentially problematic. We have chosen a strategy to couple our previous clinical experience and preclinical animal testing done at our center to develop a trial allowing the best opportunity to succeed in controlling localized prostate cancer. If this therapy is ultimately efficacious and safe, it will constitute a much more convenient non-invasive outpatient therapy as compared with current treatments. In addition to conducting a phase I/II clinical trial using SBRT for localized prostate cancer, we will also seek volunteers to take part in a companion study done in a subset of patients treated on the clinical protocol. We will tap into the strong basic science and translational science capabilities of our institution to study one of the more problematic aspects of prostate cancer therapy, hypoxia. The existence of hypoxia (low oxygen availability) to tissues and tumors within the prostate, has been implicated in several studies as a factor relating to poor outcome. We will assess the oxygen status using specialized techniques and subsequently observe how hypoxia affects outcome after SBRT.

The proposed work is innovative because it can fill a large void in understanding of a treatment that shows considerable promise in treating prostate cancers. Furthermore, this treatment, should it be effective with acceptable toxicity, could be particularly viable for an underserved population of men with prostate cancer who reside in rural, mountain, and remote areas. The work constitutes true translational science research conducted by researchers at the University of Texas Southwestern and our experienced colleagues at other centers. A trial of this design constitutes credible, prospective information. Results will be published, good or bad, which will form the basis of clinical decision making. It will serve as a springboard for further research, both in relation to clinical trials as well as basic and translational research.